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MASKLIKE FACIES WITH ASSOCIATED CONGENITAL ANOMALIES (MÖBIUS SYNDROME)

REPORT OF THREE CASES

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THE appearance of bilateral facial paralysis at birth is sometimes a perplexing problem in differential diagnosis. However, when accompanied by ocular muscle paralysis and congenital anomalies of the extremities, it then falls within the findings now known as the Möbius syndrome.

The essential features of the Möbius syndrome are as follows:

1. Unilateral or bilateral loss of abduction of the eyes.
2. Unilateral or bilateral complete or incomplete facial weakness.
3. Primary or secondary congenital anomalies of the extremities.
4. Possible other involvement of the brachial musculature.
5. Possible other cranial nerve palsies.

The condition should be diagnosed during the first few days of life because of masklike facial expression when the infant is crying, incomplete closure of the eyelids during sleep, and difficulty in nursing. It is usually mistaken at the time for pseudobulbar palsy or bilateral traumatic facial nerve palsy.

It is important that the pediatrician be aware of this syndrome in his differential diagnosis of facial diplegia. We wish to add three cases of our own to the literature on Möbius syndrome.

CASE REPORTS

CASE 1.—D. H. was brought to Children's Hospital at one week of age because of feeding difficulty and regurgitation. She was the fourth child, the other three having been normal. The prenatal period was normal. The birth weight was 7 pounds 5 ounces. The mother was 40 years of age, Rh positive, and Wassermann negative. She had hay fever and asthma. The father was 43 and well.

During delivery, the fetal head and scalp became cyanotic; the delivery was easily facilitated with forceps and the cyanosis rapidly cleared.

At birth, the facial expression was not normal, the eyes were crossed, the eyelids wide open with little tendency to blink, even after installation of silver nitrate. After feedings were instituted, the infant fed well, but regurgitated her feedings and did better on gavage feedings. The extremities

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revealed bilateral clubfeet with absence of left toes 1 and 2 and solid webbing of toes 3, 4, and 5 (Fig. 1). The right toes 2 and 3 were webbed together. The face was masklike. The mouth was small and pursed with drooping of the corners. The cry was good. The tongue showed irregular elevations and atrophy on the right side. The differential diagnosis at birth was bulbar poliomyelitis, bilateral facial paralysis possibly due to bilateral forceps trauma, or tracheo-esophageal fistula.

On the second day post partum, the infant had several convulsive seizures. A spinal puncture was negative, except for xanthochromic fluid.

The infant was transferred at one week of age to Children's Hospital. The strabismus and masklike facies had persisted. The deep and superficial reflexes were normal. The pupils reacted to light. The fundi were normal.

Fig. 1.—Clubfeet with webbing and absence of toes. Case 1.

A repeat spinal puncture was normal. X-rays with gastric tube and Lipiodol ruled out a tracheo-esophageal fistula.

The temperature was 102° F. on admission. There were rhonchi in the chest which cleared with antibiotics.

The hemoglobin was 16.5 grams, white blood count 19,500, polymorphonuclear cells 60 per cent, lymphocytes 34 per cent, monocytes 6 per cent. The urine showed a trace of albumin and a trace of sugar. The Kahn test was negative. The admission diagnosis was pseudobulbar palsy due to birth trauma and clubfeet.

The neurological findings included: third nerve, inability to adduct the eyes; sixth nerve, complete loss of abduction of both eyes; seventh nerve, bilateral complete absence of function of the muscles of facial expression; twelfth nerve, atrophy of the right side of the tongue.

At 18 months, re-examination revealed that the clubfeet were corrected, the mentality appeared normal, except for difficulty in speech. Growth and development were normal. The third, sixth, seventh, and twelfth nerve palsies persisted as at birth. The face was still masklike with pursing of the lips and drooping of the corners of the mouth (Fig. 2).

Fig. 2.—Age 18 months. Persistence of masklike facies with pursed lips and drooping of corners of mouth. Case 1.

CASE 2.—D. W. was first seen at 3 years of age. Birth was normal; mother was 37 years old at the birth of the child and had a normal prenatal period. There were no siblings. The child had considerable difficulty in feeding in infancy because of inability to suck, and gavage feedings were necessary.

Physical examination at the age of 3 revealed a masklike facies (Fig. 3). The forehead was flat. There was a wide nasal bridge with epicanthic folds. There was inability to close the lids completely and the eyes rolled upward when this was attempted (Bell's phenomenon). There was paralysis of lateral gaze and the boy turned his

head to change his field of vision. There was also paralysis of medial gaze. There was bilateral facial paralysis with inability to smile. The mouth remained open and there was a droop of the corners.

The upper extremities were normal. There was a 70 degree tibial torsion on the left with no evidence of clubfeet or webbing of the toes. There was a ¾ inch shortening of the right lower extremity with the right foot being shorter than the left (Fig. 4). There was a raised second toe of the right foot. X-rays of the pelvis revealed a bilateral coxa valga.

A diagnosis of mongolism was made in this child at infancy, both by a pediatrician and an ophthalmologist. Complete psychometric testing revealed a boy of average intelligence with difficulty only in verbal expression.

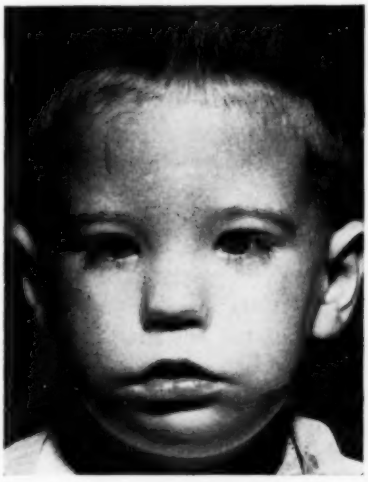

Fig. 3.—Typical masklike facies with drooping of corners of mouth, wide nasal bridge, and epicanthic folds. Case 2.

Fig. 4.—Seventy degree tibial torsion on left, ¾ inch shortening on right, and raised second toe. Case 2.

Fig. 5.—Dull, masklike facies, with drooping of corners of mouth. Case 3.

CASE 3.—R. K. was first seen at the age of 6 years at the Shriner's Crippled Children's Hospital of Los Angeles. The birth was normal and full term. The birth weight was 5 pounds 6 ounces. The infant was formula fed but had difficulty swallowing and feeding until 2 months of age, with frequent attacks of cyanosis. Bilateral strabismus was present. He was diagnosed as having an abnormal brain, and it was stated that he would not live. There was also a congenital left clubfoot.

The child was treated for two years before admission with repeated cast changes. He has been wearing a left

short leg brace for the past three years. He was operated upon five times for correction of the strabismus.

He sat up at 10 months, talked and walked at 2 years.

Fig. 6.—Inability to completely close eyelids. Case 3.

Physical examination on admission revealed a well-developed, well-nourished boy of 6 years. The face was masklike, with a dull expression (Fig. 5). The mouth was pursed with drooping of the corners. There was some impediment of speech. The pupils were equal and reacted to light. There was failure of abduction of both eyes. He could not completely close his eyes and a Bell's phenomenon was present (Fig. 6). There were no functioning muscles of expression.

Fig. 7.—Persistence of 10 degree equinus on left.

A loud systolic murmur was present over the precordium.

The left foot revealed a 45 degree metatarsus adductus with a 20 degree heel inversion and a 10 degree persistent equinus (Fig. 7).

Urine analysis and blood count were within normal range.

DISCUSSION

Facial paralysis occurring in infancy may be acquired or congenital. If the former, it is thought to be due to obstetric trauma, is almost always unilateral, and is not accompanied by paralysis of other cranial nerves.

Ante-partum compression caused by pressure of the shoulder against the head is usually unilateral and occurs in first pregnancies with large babies. Facial paralysis may also occur in intra-partum compression against bony parts of the pelvis during uterine contractions. Peripheral congenital facial paralysis may occur associated with malformation of the ears or mastoid regions. However, these cases are not associated with other oculomotor paralysis.

Pseudobulbar palsies due to brain trauma may give diffuse bilateral cranial nerve palsies, but are not associated with anomalies of the extremities.

Congenital facial paralysis is usually bilateral. Cases of congenital facial paralysis of nonobstetric origin associated with extraocular paralysis and other congenital anomalies was first described by Von Graefe[1] in 1880, and Möbius[2, 3] in 1888 and 1892, at which time he reported forty-four cases and called the condition nuclear atrophy. Other early reports of the condition, were those by Harlan[4] in 1881, Chisholm[5] in 1882, and Schapringer[6] in 1889.

Many combinations of developmental defects accompanying facial diplegia have been reported. These include paresis or paralysis of the abducens, oculomotor, motor trigeminal, glossopharyngeal, hypoglossal nerves, clubfoot, and malformations of the upper extremities and chest.

Bonnar and Owens[7] reviewed the literature and last described the clinical features in the pediatric literature in 1929. The faces of these children are motionless and devoid of expression. Speech is imperfect due to inability to use the lips. There is drooping of the angles of the mouth and constant drooling of saliva. The palpebral fissures never close completely. When the child attempts to close the lids, there is involuntary upward movement of the eyes (Bell's phenomenon). There is no discernible movement of the muscles of the face when the child cries or laughs. The inner epicanthic folds are prominent, resembling mongolism, and some of these children have been mistaken for mongolian idiots.

The pupils react to light and accommodation. The head moves in the direction of vision. The diplegia is usually noted early because of feeding difficulties and incomplete closure of the eyes. The face is masklike. There is difficulty in sucking. Crying produces a whining noise and laughter, a series of short pleasant phonations. Winking is slow and feeble.

Henderson,[8] in 1939, reviewed the literature of congenital facial diplegia, tabulating sixty-one cases. Some of these cases were facial diplegia alone. Others were associated with abducens palsy and other ocular palsies. Most of the cases, however, showed other congenital deformities, chief of these being clubfoot, syndactylism, and absence of fingers and toes. Brachial deformities and pectoral muscle hypoplasia were also observed. Of the sixty-one cases reported, all had facial diplegia, forty-five had abducens palsy, fifteen had ophthalmaplegia externa, six had ptosis, eighteen had lingual palsy, four had trigeminal palsy, twenty-three had convergent strabismus, nineteen had clubfoot, thirteen had brachial malformations, and eight had pectoral muscle defects.

All of the congenital palsies were present at birth, and remained unchanged with age.

In assessing the mental state of these children, the retarding influence of the congenital palsies was misleading. Most of the patients, however, were of normal intelligence. Henderson reported only six cases of subnormal mentality in his group, but the degree was never severe. In our three cases, the intelligence was normal, although the children appeared dull and had verbal difficulties.

In fifty-seven cases which Henderson tabulated, thirty-four were males and twenty-three females. In four instances of facial diplegia alone, two or more members of the family were affected. In true cases of the Möbius syndrome, however, with other associated congenital anomalies, there seemed to be no hereditary or familial tendency[9]

In one-third of these cases, the facial diplegia was complete, whereas when it was incomplete, the distribution was characteristic, with the perioral muscles being the least affected and the only muscles capable of any movement.

Richards,[10] in a recent article, reported three additional cases and again reviewed the literature and the theories for its etiology. Including his cases, seventy-five cases of facial diplegia have been reported in the literature, but only forty-eight are true examples of the Möbius syndrome which includes associated anomalies of the upper or lower extremities and ocular palsies.

Möbius suspected that the underlying pathologic condition was a degeneration of the nuclei of the sixth and seventh cranial nerves.

Huebner,[11] in 1900, presented the first pathological data in the autopsy report of a child aged 2 years. The post-mortem findings showed a complete absence of the nucleus of the sixth nerve and diminished number of cells of the seventh nerve nucleus. The nerve roots were small or absent.

He believed that the etiology was a brain stem hypoplasia.

While Möbius and Huebner considered the basic lesions to be a defect of ectoderm formation resulting in nuclear and nerve tissue agenesis, Lennon[12] suggested that the pathology might consist primarily of a defect in the mesoderm with a primary aplasia or agenesis of muscle with secondary degeneration of nerves.

Richards, in biopsies of the frontalis muscle of his three patients, found a total absence of muscle tissue. He agreed with Lennon, that this syndrome is due to a mesodermal defect, for the following reason.

If the condition were entirely neurological in origin, the following discrepancies arise:

1. There is usually no sensory loss over the distribution of the cranial nerves.

2. The oculomotor nerve involvement is consistently incomplete.

3. Since the upper quadrants of the face are most involved and the lower quadrant least involved, this would be impossible to explain on the basis of a neurological lesion.

4. In the development of the embryo, it is impossible to implicate a definite period of time as that when failure of development would hinder the development of both cranial nerve nuclei and the extremities.

Since in none of his cases was there any evidence of muscle in the involved areas, either degenerated or remnants, Richards agrees with Lennon's explanation of the etiology, which assigns the condition to a mesodermal defect, that is, absences of muscles with secondary failure of development of the nerves and ultimate degeneration of the nuclei as a result of disuse.

SUMMARY

Three additional cases of the Möbius syndrome are presented.

The essential features of the Möbius syndrome are:

1. Congenital facial palsy, usually bilaterial, producing masklike facies.
2. Unilateral or bilateral loss of abduction of the eyes.
3. Congenital anomalies of the extremities.
4. Possible other involvement of the brachial musculature.
5. Possible other involvement of cranial nerves.

The various theories of its etiology are presented.

The importance of differentiating this congenital syndrome at birth from pseudobulbar palsy, traumatic facial palsy, and mongolism is emphasied.

The necessity of treating most of these children as mentally normal individuals is important, despite the fact that they appear dull and have verbal difficulties.

We wish to thank Dr. George W. Westin of the Los Angeles Shriner's Hospital for Crippled Children for his cooperation in obtaining the material for Case 3.

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On Rocking

Touching the rocking of Children; some Mothers use their Children to it at the first, but others do it when they would have them sleep, and others rock them when they cry; others there are which will not use their Children to it at all, as one a Clergy Mans Wife did, who set her Child every night into a Cellar, because nothing should disquiet him in his sleep, not thinking on any other things the Child might befall, but no honest Woman I hope will imitate that fashion. In my judgement I hold it to be best, that if a Child be laid down in God's Name, &c. to rock it gently, and not too hard, then let it rest. But if a Child sleepeth unquietly being as it were frighted, as it can be perceaved, when it snorteth, snuffeth, or when frightened, or cryeth, then rock it gently again, then the melancholly blood which oppresst the Child, and frightned it, is by rocking brought to right again out of its fear and anguish, and are dispersed or expelled.

It falls out sometimes, that a Mother meaneth to quiet her Child with rocking, whereby the Child is the more unquieter, and with crying inflammed his head so vehemently, that in many daies he cannot be brought to right again: Sometimes such a Child aileth that which a Mother doth not think of, supposing it to be the Childs forwardness, which is not so, but it feeleth something to be amiss in the bed, which doth hurt it, or its hand lyeth hard, or a prick, straw, or hard feather doth prick it, or a pin, which careless Nurses left in the linnen, or a flea or louse tormenteth the Child: therefore my advice is, that if a Child will not be quieted, to take it up and see what doth ail it.

FELIX WURTZ (1518-1574)

OXYURIS VERMICULARIS: THE MOST PREVALENT PARASITE ENCOUNTERED IN THE PRACTICE OF PEDIATRICS

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INCIDENCE

PINWORM infestation has become an important and very common problem in pediatries. According to Stoll's[53] article entitled "This Wormy World," there are estimated to be 209 million persons in the world acting as hosts to the *Oxyuris* or *Enterobius vermicularis*.

There is a higher than average incidence of pinworm infestation among people who live in institutions, according to several reports cited in the bibliography.[2, 4, 7, 9, 13, 42, 45c, 47, 52] These showed that half of the children in a private school,[7] 59 per cent in a state hospital,[42] 65 per cent in a mental institution[52] were infected. Also see other studies of incidence.[5, 10, 14, 15, 21, 24, 31, 33, 41, 51, 54, 56]

Our experience showed that if one child in a family carried the parasite that siblings and parents should be examined for ova and will yield a very high percentage of positive slides.

MODE OF SPREAD

The role of animal carriers has been debated. Veterinarians report that dogs and cats do not harbor pinworms in their gastrointestinal tracts. However, we have demonstrated repeatedly that both cats and dogs may carry pinworm ova on their fur. The method we use is to stand the suspected pet on a sheet of wax paper and brush his fur. Then fold up the paper to concentrate the brushings which are picked up on Scotch tape and pasted to a slide for examination.

With household pets sharing chairs and beds as well as sleeping on the rugs, there is no mystery about their role in spreading microscopic ova from person to person in a family. This demonstration helps to correlate the apparent relationship between pets and pinworms even though the textbooks state that *E. vermicularis* is a nematode found only in man.[1-16]

Pinworm ova have been demonstrated on bedding, sleeping garments, hands, toys, furniture, and floors, and in house dust[6b] from all parts of a room occupied by an infected person. They may remain viable for days or weeks in a cool, damp place, but are rather easily destroyed by heat according to Belding.[1]

In order to develop larvae, the ova require free oxygen and human body temperature for four to six hours, according to Cram[6b] and Heller.[22] Many ova are destroyed without passing through this larva stage by the simple device of giving the infected child a morning shower bath. Those ova which develop larvae and are, therefore, infective may enter the body through the mouth aided by finger-suckers, or may be breathed into the nose on dust.

Address: 2946 Broadway.

Reardon[45b] estimated that each gravid female worm may deposit as many as 11,000 ova. The pinworm ova are microscopic in size (average dimensions 55 by 26 microns).

Worm ova pass through the stomach to be hatched in the small intestine. Adult worms inhabit the appendix, colon, and ileum, where they attach themselves to the intestinal wall. After mating, the males die and the females migrate outside to deposit their ova.

Faust[16] reports the life cycle of this parasite to require two months, while Belding[1] reports seven weeks from ingestion of eggs to the appearance of the female worm at the anus. The migration of the pinworm to the outside to lay its eggs in the folds and crevasses of the anus occurs at night while the child is asleep. The itching irritation of this activity probably causes the symptoms of restlessness and produces the nightmares suffered by the infected child. The female worm is often crushed by the scratching which the child may do in his sleep and the worm ova are easily transferred from the scratching fingers to the child's mouth, to start the chain of events again.

DIAGNOSIS

Since the female pinworm requires free oxygen for egg-laying,[1] examination of stools may not find ova in an infected person.

Study of perianal material is a much more accurate method of finding worm ova. Use of the NIH swab developed by the National Institute of Health at Bethesda, Maryland,[18] is a very good method. It is described in detail by Wood.[59] Other methods are described by Hall,[20] Podyapolskaya,[43] Sawitz and associates,[48, 49] Schuffner and Swellengrebel,[59] and von Hofe.[55] Graham[19] uses Scotch tape to pick up worm ova. The parent is instructed to hold a three-inch loop of transparent Scotch tape over the forefinger, or over the end of a tongue depressor, with the smooth side toward the finger and the sticky side outward. The adhesive side of the tape is then pressed into the perianal folds of the skin to pick up the worm eggs. The Scotch tape is then smoothed down on a glass slide and sent to the laboratory. Ova and worms are identified easily under a microscope. The Scotch tape smear must be made the first thing in the morning before the child is up and dressed. This method is simple, practical, and accurate.

SYMPTOMS AND PATHOLOGY

Culbertson[11] stated that "nervous symptoms are frequently noted in infected persons if there is sufficient erosion of the intestinal mucosa to expose sympathetic nerves. Insomnia is common, and even epileptiform symptoms may develop. An intense and aggravating pruritis ani is usual, especially at night after the person has retired. Occasionally the worms cause vaginitis in women."

Pinworms are sometimes found by accident in children who display no symptoms, as, for example, when the appendix is filled with worms at the time of an appendectomy. Finding pinworms in appendices has been reported by several authors.[17, 26, 30, 46] Vague gastrointestinal symptoms in children are frequently dismissed without considering the possibility of pinworm infection, and yet these worms have been found in the nose,

esophagus, and stomach, as well as throughout the bowel.

Behavior symptoms in children have been described by many authors[6b, 32] and include nail biting, thumb-sucking, nose picking, grinding of teeth at night, nightmares, restlessness, inattention, poor cooperation, scratching of anus, and irritability.

PREVENTION

Viable eggs must be destroyed in a household where a patient has the infection, to prevent constant reinfection. Methods of sterilizing the patient's clothing, bedding, towels, toys, furniture, and bathroom fixtures must be carried out. House dust may carry the eggs, as reported by Nolan and Reardon.[40]

Sunlight and ultraviolet lamp radiation are very valuable in destroying eggs. While cool, moist conditions favor their survival, according to Cram,[6b] Heller[22] believes that sufficient ventilation and drying of rooms will kill most of the eggs. Wood[59] says for practical purposes in the average home, washable articles should be laundered in very hot water. Dry oven heat would sterilize nonwashable toys. Rugs, furniture, and drapery should be sunned on a dry, hot day. The vacuum cleaner will pick up some eggs. Separate wash cloths and towels for face and body would safeguard autoinfection. Toothbrushes should not be exposed to bathroom dust. Strict personal cleanliness and keeping the children's fingers out of their mouths would prevent reinfections.

CONTROL

The public health control would necessarily include: (1) treatment of infected persons, (2) ridding environment of eggs, and (3) educating the public on how the infection is spread and how to avoid it.[8, 12, 23, 25, 27, 29, 34, 39, 44, 57, 58]

OXYURIASIS IN OFFICE PRACTICE

The incidence of oxyuriasis in our office practice at the Redwood City Clinic was not determined, since we made no systematic study of consecutive cases. However, NIH anal swabs[18, 19] were studied on all children whose symptoms warranted the Scotch tape method of investigation.

Of these selected cases, 80 per cent carried pinworm ova, while further anal swabs on siblings and parents of these children yielded 72 per cent positives.

We have tried a variety of widely used[3] treatments without achieving outstanding satisfactory results.

Table I summarizes 335 proved cases of pinworm carriers treated by various drugs.* Cures were meas-

TABLE I. TREATMENT OF OXYURIASIS IN OFFICE PRACTICE

	NUMBER OF CASES	DIPHENAN	GENTIAN VIOLET	TERRAMYCIN	CRYSTOIDS ANTHELMINTIC	ANTEPAR
Ages under 5 yr.	150	40%	44%	50%	Not used	85%
Ages 6-10 yr.	135	36%	62%	60%	42%	80%
Ages 11-16 yr.	50	34%	60%	66%	50%	86%
Length of treatments given		10 da.	21 da.	3-4 da.	1 dose	14 da.

Percentage of cases cured measured by negative smears after cessation of symptoms.

*Syrup of Antepar, kindly supplied for our experimental use by Burroughs Wellcome & Co., yielded by far the best results in our series. We followed the manufacturer's recommendations on dosages of all drugs used.

ured by obtaining two negative anal swabs, one and two months after cessation of symptoms.

Parents express many different attitudes toward "having worms," from one extreme, "it just couldn't happen to us, we're clean," to indifference, "all children have worms, so what." Some people have to be convinced that there is no disgrace about having worms (only in keeping them).

Certain generalizations may be made:

(1) The condition is very common.
(2) It undermines general health through lack of sleep and nervousness.
(3) It may be acute.
(4) It can be cured.
(5) It tends to recur.
(6) It affects all social levels.
(7) It is usually a familial disease.

CONCLUSIONS

1. Oxyuriasis is a very common problem in pediatric practice.

2. The role of household pets in spreading pinworms is demonstrated.

3. Literature concerning the life cycle of oxyuris vermicularis and public health control of this parasite is reviewed.

4. Methods of diagnosis and treatment are discussed.

5. A summary of 335 cases of pinworm infestation treated in office practice is presented.

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CHONDROECTODERMAL DYSPLASIA

Report of a Case and Review of the Literature

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A SYNDROME characterized by ectodermal dysplasia, polydactyly, chondrodysplasia, and congenital heart defect was first described by Ellis and van Creveld[1] in 1940. These authors suggested the name "chondroectodermal dysplasia" for this syndrome. Their original report included three cases, one of which was described originally as a separate case by McIntosh[2] in 1933. No further cases were described until 1952 when Caffey[3] reported two new cases and a follow-up study of the case previously reported by McIntosh and Ellis and van Creveld. Keizer and Schilder[4] reported an incomplete case of this syndrome without polydactyly. The case presented in this communication has all the typical characteristics of the syndrome as originally described by Ellis and van Creveld and further by Caffey. It is the sixth complete case to be reported in the literature. The diagnosis in this case was made at birth in the Hunter Air Force Base Hospital nursery, Savannah, Georgia.

CASE REPORT

M. G., a 6-month-old white male infant, was born by uneventful spontaneous delivery on Oct. 15, 1953. The mother was 21 years old and a primigravida. The father was 22 years of age. There was no history of congenital malformations in the family, nor was there any history of consanguinity. The birth weight was 6 pounds 11½ ounces. The general condition at birth was good. The cry was lusty, and there was no cyanosis present.

Physical examination during the first twenty-four hours following birth revealed multiple deformities. The upper and lower extremities were absolutely and relatively short in comparison to the length of the trunk. There were six fingers on the right hand and seven fingers on the left hand with a syndactyly of the sixth and seventh fingers. There were five toes on each foot. A left talipes equinovarus was present (Figs. 1 and 2). The fingernails and toenails were markedly hypoplastic, appearing to be tiny, scaly fragments. Examination of the penis revealed an epispadias. Two small upper premolar deciduous teeth were erupted at birth and two lower premolars were bulging in the gum and nearly erupted. The latter finally erupted in the second week of life. The only other findings present were a protuberant abdomen with palpable hepatic edge and splenic tip. No cardiac murmur was heard at birth.

Body measurements at birth were as follows: total length 47 cm., head circumference 34.5 cm., chest 30 cm., abdomen 30.5 cm., distance from umbilicus to heel 20 cm., length of upper extremity (acromion to radial styloid) 10 cm., lower extremity (anterosuperior iliac spine to heel) 18.5 cm. Laboratory findings were as follows: urine, negative; complete blood count, normal; serology, negative. Roentgen examination of the long bones and skull revealed classic changes consistent with a marked chondrodysplasia. In view of these findings, a tentative diagnosis of

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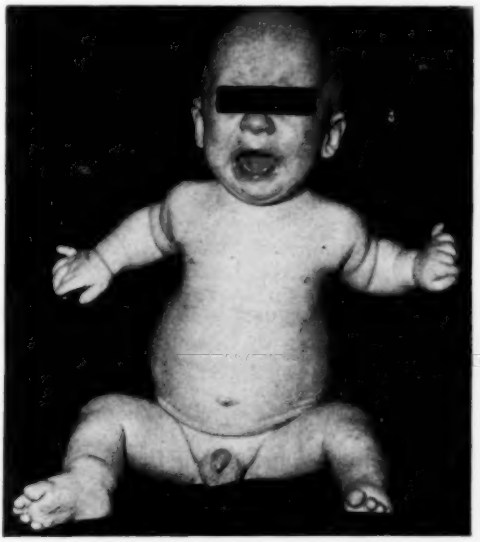

Fig. 1.—Photograph at 3 months of age demonstrates short, thick extremities and normal trunk and head. The polydactylism is clearly visible. The left talipes equinovarus is also noted.

Fig. 2.—Roentgenograms of legs. At birth, the left talipes equinovarus is noted. The tubular bones are short and thick; there is disproportionate shortening of the fibulas. Proximal ends of both tibias are widened and slight pointing is visible. No polydactylism or syndactylism is present in the feet.

chondroectodermal dysplasia (Ellis-van Creveld syndrome) was made on the second day of life.

On the third day of life the stools were noted to be very light in color and the urine was dark amber in appearance. Stool examinations were negative for bile and urobilinogen, while the urine was positive for bile and negative for urobilinogen. The child did well clinically otherwise, took his feedings well, and was discharged from the nursery on the fifth day of life. He was not abnormally jaundiced. Follow-up questioning of the mother revealed that the urine gradually became lighter in color and the stools began to take on a yellow color at about 2 weeks of age.

Since birth, the child has had five additional hospital admissions. The first was at 2 weeks of age because of a severe upper respiratory infection accompanied by choking, cyanosis, and dyspnea. He made an uneventful recovery after three days of treatment with penicillin and streptomycin. On this admission, it was also noted that the liver had enlarged to three fingerbreadths below the costal margin, whereas the edge of the liver had been just palpable at birth. There was no icterus. An electrocardiogram was negative.

The second admission was three days later for a similar picture of severe nasal congestion and rib retractions. He was again started on penicillin and streptomycin and the respiratory infection gradually cleared within a week. Because of the marked retractions and choking accompanying both respiratory infections, a barium study of the esophagus was done on this admission and revealed no abnormalities. Cardiac fluoroscopy revealed normal cardiac outline, rate, and rhythm, without evidence of specific chamber enlargement. The liver was still markedly enlarged. Blood chemistries revealed the following: serum bilirubin, 2.8 mg. per cent; direct bilirubin 1.24, indirect 1.55; cholesterol, 180 mg. per cent. Urobilinogen was found in the stool and the urine was negative for bile. The child was discharged after one week in apparently good condition.

The third hospital admission was at one month of age because of severe vomiting and diarrhea of three days' duration. The general condition on this admission was poor. Physical examination revealed him to be markedly lethargic, moderately icteric, and moderately dehydrated. The temperature was 102° F. A spinal tap done on admission was negative. After two days of treatment with subcutaneous fluids, tea, penicillin, and streptomycin, his condition improved, and milk feedings were again resumed. However, on the fourth hospital day he again spiked a high fever and the diarrhea resumed. He became rapidly dehydrated and was further treated with intravenous fluids and blood. The icterus became more marked during this hospital stay and the liver remained enlarged, while the edge of the spleen remained palpable. Laboratory findings on this admission were as follows: urine, positive for bile, positive for urobilinogen; total serum bilirubin, 8.3 mg. per cent; direct bilirubin, 7.0 mg. per cent; indirect bilirubin, 1.3 mg. per cent. Two weeks later, prior to discharge, total serum bilirubin dropped to 5.4 mg. per cent. Alkaline phosphatase was 6.7 B.U. Cephalin flocculation was one plus and the thymol turbidity was 1.0 units. Stool cultures were negative and no ova or parasites were found. It was felt that the child probably had had an exacerbation of an infectious or toxic hepatitis during this illness from the original episode in the neonatal period.

The fourth hospital admission was at 2 months of age for another severe upper respiratory infection and bronchitis. He was treated with penicillin and made an uneventful recovery in five days.

The fifth hospital admission was Dec. 26, 1953, at 2½ months of age.

He was admitted for another attack of choking, cyanosis, and apnea, due to marked nasal congestion associated with the onset of another respiratory infection. It was at this time that a loud, blowing systolic murmur was first heard over the precordium, loudest at the left third and fourth intercostal spaces. The second pulmonic sound was louder than the second aortic sound. It was felt that the child had a congenital malformation of the heart, most probably an interventricular septal defect, in addition to his other anomalies. Repeat chest x-rays revealed a normal heart shadow and a repeat electrocardiogram was normal. On this admission, the upper respiratory infection cleared rapidly, but the patient developed another bout of diarrhea on the third hospital day, which cleared completely in one week on appropriate therapy. Since discharge, his stools have been completely normal and his general condition during the following three months has remained excellent. The body measurements from this admission revealed that he was growing at a fair rate but that his arms and legs were still relatively and absolutely short compared to the trunk. His total length was 59 cm.; head circumference 40.5 cm.; crown to rump 39.2 cm., and umbilicus to heel distance 23.3 cm. Liver studies on that admission revealed that the serum bilirubin had dropped to 3.5 mg. per cent and that the cephalin flocculation was two plus. At 4½ months of age, he weighed 13 pounds, and his clinical condition was good. His appetite was excellent and stools normal. His development was progressing normally in all spheres and his intelligence appeared to be normal. At present, he is being treated with a cast for his left talipes equinovarus. A total of five small, malformed teeth have erupted to date and have all fallen out. Removal of the extra digits of the right and left hands was carried out at the age of 9 months. Pathologic study of the bone and cartilage removed revealed no abnormalities.

Radiologic Features.—We have had the opportunity of following this case since birth. Serial roentgen examinations have been made. All the tubular bones are short and thick and the progressive distalward shortening of the tubular bones of the upper extremities has been apparent since birth and has increased in degree to the time of this report.

Fig. 3.—Roentgenogram of right upper extremity. At 5½ months, the slope of the proximal humeral head is most apparent laterally. The thickening of the proximal ulna and distal radial surfaces is striking, as is the relative hypoplasia of the distal ulna and proximal radial ends. The fifth and sixth metacarpals are fused, and their medial surface is concave. Proximal phalanges are short and thick with cupped bases and relatively huge ossification centers in second through fifth digits. No ossification centers have appeared in the middle phalanges; these are also short and thick.

Measurements of the various tubular bones compared to median values given by Maresh[5] reveal that, in this instance, the humeral shaft measures

58 mm. or 65 per cent of normal; radius is 42 mm. or 60 per cent of normal; ulnas 51 mm. or 65 per cent of normal. The femoral shafts measure 78 mm. or 69 per cent of normal; the tibias measure 56 mm. or 62 per cent of normal; the fibulas measure 45 mm. or 52 per cent of normal. The greatest relative shortening is therefore in the fibulas, as in the previously reported instances of chondroectodermal dysplasia.

Fig. 4.—Roentgenogram of the thorax. At birth, the ribs are short and thick; their ends are blunted and curved inferiorly. The cardiac shadow is within normal limits. The proximal humeral ends are thickened, and there is definite peaking of the proximal ends with ectopic ossification centers.

Multiple deformities were present in the hands, including supernumerary digits and syndactyly and synmetacarpalism. Delayed skeletal maturation is visible throughout. The changes in the proximal and distal ulnas and radiuses are striking (Fig. 3), as are the peaking and lateral slope of the proximal humeral and tibial shafts (Figs. 2, 3, 4, and 5).

COMMENT AND DISCUSSION

As originally described by Ellis and van Creveld, the clinical features of the syndrome of chondroectodermal dysplasia include the following tetrad: chondrodysplasia, ectodermal dysplasia, polydactyly, and congenital morbus cordis. Ectodermal dysplasia usually includes tiny, deformed fingernails, dysplasia of the teeth, and perhaps fine, scanty hair. Besides having the above classical

Fig. 5.—Roentgenogram of lower extremity. At 4 months, all the tubular bones are short and thick. The fibular foreshortening is now apparent, as is the peaking of the proximal tibial shaft. No proximal tibial ossification center has appeared. The distal femoral ossification center has now appeared.

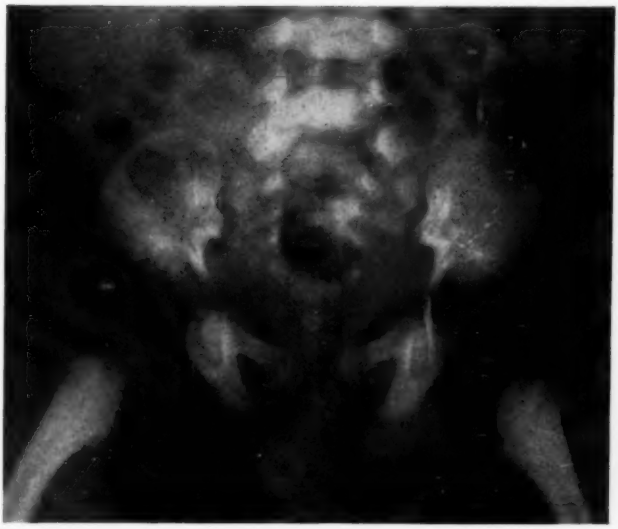

Fig. 6.—Roentgenogram of the pelvis. At birth, the proximal ends of the femurs are rounded and thick. The acetabular cavities are hypoplastic and irregular in outline.

Fig. 7.—Roentgenogram of the left hand. At 5½ months, similar changes are noted to those in the other hand. Seven digits are present in this hand with synmetacarpalism of the fifth, sixth, and seventh metacarpals. A single carpal ossification center has appeared in each hand. Maturation of the proximal phalangeal ossification centers is accelerated.

features, the patient here presented also has an epispadias, which is an additional ectodermal anomaly, and a talipes equinovarus, which is probably an incidental anomaly. A feature described in four of the five previous cases, which is not present in this case, is fusion of the upper lip and gum pad. In addition, a moderate degree of acetabular hypoplasia is noted (Fig. 6), which has been present in only one of the previously reported cases. In this instance, the left hand exhibits seven digits; a maximum of six has been reported in all previous instances.

It is not possible to show any sex disposition, four of the five previously reported cases being females and the present case being the second male. It is suggested that this syndrome is a recessive, inherited defect without sex linkage. Consanguinity (mother and father first cousins) was present in two of the three cases originally presented by Ellis and van Creveld.

It is interesting to note that, in addition to the anomalies common to this syndrome, the present case exhibits hepatosplenomegaly. However, because of the clinical course previously described, it is felt that this rather severe hepatomegaly was due to a neonatal infectious or toxic hepatitis rather than to a congenital anomaly.

Dwarfism in these cases is due to a relative and absolute shortness of the bones of the extremities rather than to any diminution in length of the trunk. The roentgenographic abnormalities in this case are similar to those previously described. They include:

1. The tubular bones of all the extremities are short and thick. There is a progressive distalward shortening of the tubular bones, the most shortened bone of all being the fibula in this case and in all the previously reported instances. The peaking of the proximal tibial and humeral shafts with lateral and medial sloping, the former being more prominent, it most striking in this instance (Figs. 2, 3, 4, and 5).

2. Retarded skeletal maturation is noted. Much of this may well be attributed to the stormy neonatal period. The distal femoral secondary ossification center, as well as the proximal tibial secondary ossification center, are delayed in appearance. The former did not appear until the age of 4 months (Fig. 5).

3. The metacarpals and phalanges are short and thick and the ossification centers for the proximal phalanges in this case are relatively enormous and indicate accelerated skeletal maturation in the proximal phalanges. There is definitely diminished skeletal maturation of the distal phalanges (Figs. 3 and 7). In the left hand, in this instance, a fusion of three metacarpals, rather than the two previously reported as the maximum, is noted (Fig. 7).

4. Hypoplasia of the acetabular cavities of the pelvis has been present in one previous instance.[1, 2]

The prognosis in this syndrome probably depends on the severity of the malformations. As far as the previous cases have been followed, there has been no mortality. However, one of Caffey's patients was doing quite poorly at 14 months, suffering from an apparently severe congenital malformation of the heart.

At 9 months, our patient is doing quite well clinically, in spite of having had a relatively stormy first three months.

All the patients in the reported cases have apparently had a normal mental development. The 19-year-old female followed by Caffey was a college graduate. The child herein reported is very alert and of apparent normal intelligence.

SUMMARY

1. A case of chondroectodermal dysplasia (Ellis-van Creveld syndrome) is presented as an additional case to the five cases previously reported. The literature is reviewed.

2. The deformities present in this case, which are characteristic of this syndrome, are chondrodysplasia, resulting in dwarfism, with progressive distalward shortening; polydactyly; syndactyly, synmetacarpalism; dysplasia of the teeth and fingernails; congenital malformation of the heart, most probably an interventricular septal defect.

3. Additional malformations present are talipes equinovarus and an additional ectodermal malformation, epispadias.

4. The characteristic roentgenologic features as described by Caffey are presented and described in this instance with additional findings.

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PERFORATION OF THE STOMACH IN THE NEONATAL PERIOD

Report of a Survival in a Premature Infant

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PERFORATION of the stomach in the newborn infant has not been emphasized as a pediatric problem, whose successful treatment depends on early diagnosis. At least twenty-nine cases of perforation have been reported, many of these being found at autopsy. In 1950, Leger and associates,[1] in Canada, successfully closed a perforation of the stomach in a 6-day-old infant. Kellogg and co-workers,[2] reported a second survival and more recently Northway and associates[3] reported the third infant to survive a perforation of the stomach, with surgical closure.

The purpose of this paper is to present a case of perforation of the stomach in a premature infant who survived with successful closure of the perforation.

CASE REPORT

Baby boy B. C. was born by cesarean section at the Medical College of Virginia Hospital on June 21, 1954. Repeat cesarean section was done before active labor because of a previous section, and the presence of a borderline pelvis. The birth weight was 4 pounds 15½ ounces, length 18¼ inches, and head 12½ inches. The original physical examination when the infant was about ten minutes of age was made in the premature nursery. Gastric suction had been carried out in the delivery room. There were no gross abnormalities. The baby had a bruised upper lip, the soles of the feet were bruised, and over the left anterior chest wall, extending almost to the abdomen, was an ecchymotic area. The baby had good color and cry, and the remainder of the examination was negative.

Oxygen, vitamin K, frequent turning, and hourly stimulation were given. At 24 hours of age, 5 per cent glucose was started by mouth, and the baby took this normally, though not eargerly, spitting up mucus frequently. At 60 hours of age, weight 4 pounds 14 ounces, the infant seemed vigorous and hungry, and a powdered milk preparation was started. He took this without relish, frequently took less than 30 c.c., and the nurses noted that he would spit up "soured milk" from one feeding to the next. Meconium stools were passed normally, and, later, transitional stools were seen. On the fourth day of age, an Olac formula was started at 26 cal. per pound and parenteral fluids were given. The baby did not eat eagerly at any time, and continued to spit up between feedings. There was no prominent jaundice or temperature elevation.

On the night of the fifth day of age, the infant refused several feedings and seemed listless. Penicillin aqueous, 100,000 units every twelve hours, had been ordered, empirically, that morning. On the morning of the sixth day of age the abdomen was distended and tense, but bowel sounds were audible at times, and there was no temperature elevation. The child's color was poor and he would not eat. The skin of the upper abdomen showed pitting edema and he appeared jaundiced.

An upright film of the abdomen was done (Fig. 1) and obvious air was

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seen under the diaphragm and free air was present in the abdomen. Thin barium by rectum flowed freely to the sigmoid. The white blood cell count was 8,600 and the hemoglobin was 13.8 grams. Fifty-two per cent of the white cells were polymorphonuclears. Surgical consultation was obtained at once, and laparotomy was carried out approximately three hours after the condition of the infant was noted. The abdomen was opened through a transverse incision, and the recti were retracted. Free air was found in the abdominal cavity and there was hyperplastic peritonitis in the entire upper abdominal region. There were milk curds in the abdomen. Exploration revealed a perforation in an area which looked necrotic on the anterior surface of the stomach near the greater curvature, at the junction of the upper and middle thirds of the stomach. This necrotic area measured about 3 cm. in greatest diameter and the perforation was about 4 mm. in diameter. The area of necrosis was resected and the defect closed with a continuous lock suture of No. 00 chromic catgut, reinforced with interrupted fine cotton sutures. The incision was closed in layers, peritoneum being closed with a continuous suture of No. 00 chromic catgut, and the fascial layers, subcutaneous tissue, and skin closed with interrupted cotton sutures. No wound drainage was used.

Postoperatively, Wangensteen drainage was carried out for twenty-four hours, two small blood transfusions were given, and glucose by mouth was taken forty-eight hours postoperatively. Weak Olac feedings with clyses of parenteral fluids were necessary for several days. The blood chemistries forty-eight hours after surgery were: Na 140 meq. per liter, Cl 110 meq. per liter, K 5.5 meq. per liter, CO_2 combining power 29.5 meq. Hemoglobin was 8 grams.

Slow but progressive improvement continued. Penicillin, streptomycin, and erythromycin were used in postoperative management. On the sixteenth day of age the baby weighed 4 pounds 9 ounces, and took 30 c.c. of formula every three hours. The wound healed per primum.

The infant was discharged on the twenty-eighth day of age at 5 pounds 3 ounces, and, at home, gained a pound in two weeks.

DISCUSSION

Most of the earlier cases of perforation of the stomach were found to be due to peptic or duodenal ulcer. Thelander and Mathes[4] reviewed this subject thoroughly, and Kellogg and associates[2] in 1951 reported a survival in an infant with this etiological factor.

In 1943, Herbut[6] pointed out another possible cause of perforation of the stomach, i.e., a congenital defect of the musculature of the stomach, leading to perforation, and Griffin and Griffin[7] found this situation in their patient reported in 1954. Northway's[3] successful surgery was on such an infant.

A third possible contributing factor to gastric perforation is the presence of other defects such as atresia of the pylorus or duodenum, and with the great dilitation of the stomach because of these anomalies, perforation occurs. One of the infants reported by Greene and Gose[8] illustrated a duodenal stenosis with secondary perforation of the stomach, and Burnett and Halpert's[9] patient had atresia of the pylorus.

Mechanical injury from gavage feedings, neonatal asphyxia, embolism, thrombosis, vascular disease and sepsis have also been mentioned as possible causes for a gastric perforation.

The signs and symptoms of a perforation of the stomach are very similar, no matter the basic cause. The

Fig. 1.—Pneumoperitoneum with air under diaphragm.

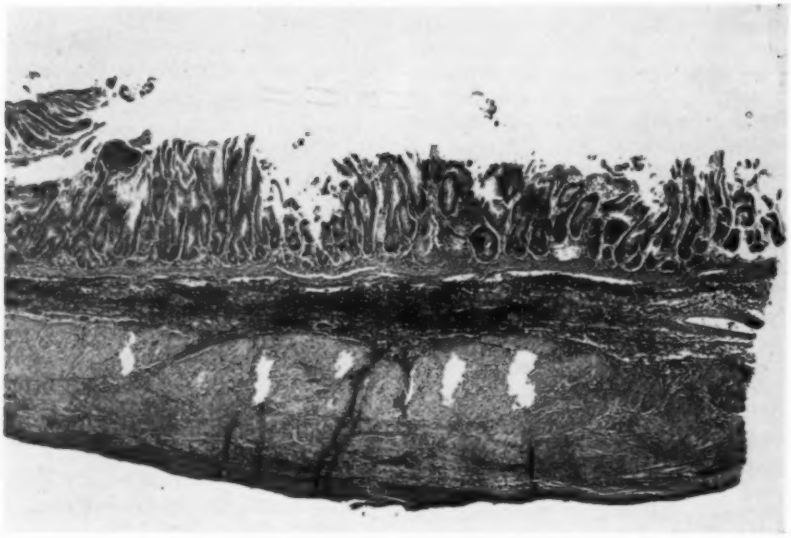

Fig. 2.—Antral stomach wall with perigastritis.

infants usually eat poorly, frequently spit up for several days preceding the acute perforation. In those with ulcer as the cause, melena and hematemesis may be noted. With the acute perforation, pallor, lethargy, shock, and a variable amount of abdominal distention occurs. The stomach may be relatively soft, and the percussion note may be tympanitic over the upper or mid-abdomen. Free fluid has at times been demonstrable in the abdomen. Fever is not remarkably present, nor is leukocytosis or a granulocytic increase. Anemia may be prominent if an ulcer has bled. The most valuable single diagnostic aid is the upright film of the abdomen. Finding of pneumoperitoneum and free air under the diaphragm confirms the diagnosis of a ruptured viscus. Some have found Lipiodol swallow harmless and helpful in localizing the area of the perforation.

Treatment is early surgery, with general supportive measures, transfusions, and appropriate antibiotics.

The pathology found varies with the etiological condition. In this case, pathological section showed an intact mucous membrane, with normal thickness of all coats. The outer muscle layer and subserosa were thickened by inflamed granulation tissue. There was an exudate of polymorphonuclear leukocytes on the external surface.

In this case, as in five others in the literature, as pointed out by Fomon and co-workers,[10] there was no actual demonstrable peptic ulceration. The exact cause in this case must have been related to trauma (ecchymosis on left anterior chest wall, lips, etc.). The gastric suction employed once in the delivery room seems innocuous, since it is a common procedure in infants delivered by cesarean section and in those born of diabetic mothers.

SUMMARY

1. A case of rupture of the stomach in a 5-day-old premature infant, who survived, is presented.

2. Causes of perforation of the stomach are discussed and aids in diagnosis, including x-ray, are given. The treatment and pathological findings are included in the discussion.

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AN EPIDEMIOLOGICAL STUDY ON PSEUDOMONAS AERUGINOSA (BACILLUS PYOCYANEUS) IN PREMATURE INFANTS IN THE PRESENCE AND ABSENCE OF INFECTION

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IT HAS been known for more than half a century that *Pseudomonas aeruginosa (Bacillus pyocyaneus)* occasionally causes infection in man, either primary or secondary. The literature has been reviewed in 1933 by Epstein and Grossman[1] and, more recently, in 1946 and 1947, by Robitzek and Prausnitz[2] as well as by Stanley.[3] This microorganism is found in polluted water and sewage and is encountered occasionally in the intestinal tract and on the skin of human beings without evidence of infection. In recent years, because of the relative resistance of this bacterial species to chemotherapeutic agents and antibiotics, *Ps. aeruginosa* infections have been encountered relatively more frequently than in the preantibiotic era. When *Ps. aeruginosa* was isolated on routine cultures from premature infants in June, 1951, it was decided to carry out a systematic investigation into its presence in the upper respiratory tract, feces, and on the skin of premature infants, and to correlate its presence or absence with the clinical course. This study also afforded an opportunity to investigate the question as to the relationship between administration of ACTH and development of infection in carriers of this bacterial species; ACTH was given at that time for the treatment of retrolental fibroplasia. Finally, it was of interest to study the presence of *Ps. aeruginosa* in the upper respiratory tract, since this bacterial species has been incriminated as cause of diarrheal disease and other enteric pathogens (salmonellae, shigellae, and *Escherichia coli* serogroups 111, 55, and 26[4-7]) have been isolated from the nasopharynx and/or throat. The results of these investigations form the basis of the present report.

MATERIAL AND METHODS

All patients studied were admitted to the Premature Unit of the Children's Hospital, which accommodates up to twenty-three infants and which is separate from both pediatric and maternity units.

The unit is staffed by graduate nurses with specialized training in premature infant care and student nurses under supervision of the head nurse of the premature unit. All nurses in the unit work only there and are not rotated to other divisions of the hospital. All infants housed in the unit are in individual cubicles, in either Isolette, Gordon-Armstrong incubator, or bassinet. Individual gown technique is maintained for each cubicle. In general, the medical and nursing care of

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the unit corresponds to standards of the American Academy of Pediatrics.[8] The unit is supervised by one pediatrician (D.H.W.).

Cultures from skin (buttocks), nasopharynx, throat, and rectum were obtained twice weekly. The specimens were seeded immediately on brain veal and Endo agar as well as in infusion broth; these culture media were then incubated at 37° C. for eighteen to twenty-four hours. The broth was subcultured on brain veal and Endo agar. The agar plates were examined for the presence of *Ps. aeruginosa*, and the relative and absolute number of *Ps. aeruginosa* colonies were noted. This microorganism is readily recognized by its typical growth, pigment formation, and odor on agar. Wherever necessary, the biochemical activities, such as gelatin liquefaction and sugar fermentation, were studied.

RESULTS

A total of 143 premature infants was studied with respect to the presence of *Ps. aeruginosa* on the skin, in the nasopharynx, throat, and feces. The results are summarized in Table I.

Table I shows that, depending upon the type of specimen studied, the microorganism was demonstrated in 25 to 51 per cent of these patients. It was encountered more frequently in the feces and throat than on the skin and in the nasopharynx.

In order to obtain information regarding the first appearance of this microorganism after admission to the premature unit, the data on these 141 infants were analyzed. The bacteriological study was commenced on the first day of admission in nineteen infants, on the third or fourth day in thirty-nine infants, and after the fifth day in eighty-three infants. In a few patients some of the specimens were not obtained. Data on the first appearance of *Ps. aeruginosa* in relation to the time elapsed after admission are summarized in Table II.

Perusal of Table II reveals that none of the infants of the first group harbored *Ps. aeruginosa* in the throat and nasopharynx or on the skin on the day

TABLE I. PS. AERUGINOSA IN PREMATURE INFANTS

SPECIMEN	NUMBER AND PERCENTAGE OF CASES	
	HARBORING PS. AERUGINOSA	NOT HARBORING PS. AERUGINOSA
Skin	35 (25%)	107 (75%)
Feces	73 (51%)	70 (49%)
Nasopharynx	38 (27%)	104 (73%)
Throat	57 (40%)	86 (60%)

TABLE II. APPEARANCE OF PS. AERUGINOSA IN PREMATURE INFANTS

SPECIMEN	NUMBER AND PERCENTAGE OF PATIENTS		
	DAYS AFTER ADMISSION		
	1ST DAY	3RD TO 4TH DAY	5TH TO 14TH DAY
Skin	0/14* (0%)	8/37 (21%)	9/77 (12%)
Feces	1/14 (7%)	17/36 (47%)	18/70 (26%)
Nasopharynx	0/19 (0%)	6/38 (16%)	14/83 (17%)
Throat	0/19 (0%)	14/39 (36%)	13/83 (16%)

*Numerator = Number of patients harboring *Ps. aeruginosa*.
Denominator = Total number of patients.

of admission and that in only one patient was this microorganism present in the feces. In contrast, among thirty-nine infants first studied bacteriologically on the third or fourth day following admission from 16 to 47 per cent of the patients harbored this microorganism. In an additional group of eighty-three infants culturally examined for the first time between the fifth and fourteenth day after admission, this bacterial species was recovered in 12 to twenty-six per cent of these cases. These data suggest that exposure to *Ps. aeruginosa* was followed within a few days by the appearance of this microorganism in a relatively large number of premature infants in a nursery unit.

Data on the duration of the carrier state of the microorganism are recorded in Table III.

Obviously, it was of importance not only to determine the presence or absence of *Ps. aeruginosa* in these premature infants, but also to obtain a quantitative appraisal. This estimation is based on both the absolute and relative number of colonies of *Ps. aeruginosa* which grew on the primary solid isolation culture media. Clearly, this relative quantitative appraisal pertains only to nonfastidious bacteria which grow on brain veal and/or Endo agar under aerobic conditions. Table IV summarizes the pertinent data.

Inspection of Table IV reveals that large numbers of *Ps. aeruginosa* were more commonly found in feces, nasopharynx, and throat than on the skin.

At the time this investigation was terminated (May, 1952) the incidence of *Ps. aeruginosa* in premature infants had declined considerably, and, during the ensuing two years, this bacterial species has been encountered only sporadically.

It is interesting to note that on several occasions this microorganism was recovered from the air in the nursery by means of the electrostatic air sampler.

Clinically, the majority of these premature infants did not have infection

TABLE III. DURATION OF PS. AERUGINOSA CARRIER STATE IN THIRTY-FIVE PREMATURE INFANTS

SPECIMEN	NUMBER OF PATIENTS CARRYING PS. AERUGINOSA FOR			
	4 DAYS	7 DAYS	10 DAYS	14 DAYS
Skin	12	11	1	1
Feces	0	7	9	19
Nasopharynx	2	9	11	4
Throat	1	2	6	21

TABLE IV. QUANTITATIVE ESTIMATION OF PS. AERUGINOSA IN PREMATURE INFANTS

SPECIMEN	TOTAL NUMBER OF PATIENTS	NUMBER AND PERCENTAGE OF PATIENTS HARBORING PS. AERUGINOSA ORGANISMS		
		NO	FEW	MANY
Skin	142	107 (75%)	27 (19%)	8 (6%)
Feces	143	70 (49%)	49 (34%)	24 (17%)
Nasopharynx	142	104 (73%)	15 (11%)	23 (16%)
Throat	143	86 (60%)	27 (19%)	30 (21%)

It is clearly evident from Table III that a relatively large number of infants harbored this microorganism in the feces and in the throat for at least two weeks. In contrast, the carrier state of the skin lasted a shorter period of time in the majority of infants. The data on the duration of the carrier state of the nasopharynx are less clear-cut.

attributable to *Ps. aeruginosa*. Only a few patients had pustules of the skin, mild diarrhea, or bronchopneumonia which may conceivably have been associated with this microorganism. On the other hand, there were five patients (four of whom succumbed) who suffered from generalized *Ps. aeruginosa* infection. A brief résumé of these cases follows herewith.

CASE REPORTS

CASE 1.—K. R., a male premature infant, who weighed 1,560 grams at birth, had a normal clinical course until the fifth day of life, when he became deeply jaundiced, developed generalized petechiae, respiratory distress, and emesis of feedings. Throat, nasopharyngeal, and blood cultures at the onset of illness revealed the presence of *Ps. aeruginosa* in large numbers. The infant died on the sixth day of life. Post-mortem examination revealed in addition to a recent left cerebral hemorrhage, recent pneumonia, peritonitis, and pericarditis.

CASE 2.—D. H., a premature male infant, weighing 1,575 grams, was admitted to the hospital twelve hours after birth with an omphalocele; the membrane covering the abdominal contents had ruptured en route to the hospital, exposing the stomach and intestinal tract, which were covered with meconium. The abdominal defect was repaired surgically, and despite the rather extensive procedure the infant's postoperative condition was surprisingly good. However, on the seventh postoperative day, the respirations became labored and rapid and shortly later ceased altogether. A blood culture drawn moments before death revealed innumerable colonies of *Ps. aeruginosa*. Chloromycetin and penicillin had been given from admission to death. Post-mortem examination revealed evidence of septicemia, multiple pulmonary abscesses, myocarditis, and recent fibrinous peritonitis. The microorganism was isolated together with pneumococcus from a lung abscess.

CASE 3.—R. S., a premature female infant, weighing 936 grams at birth, developed stages I and II of retrolental fibroplasia between the fortieth and forty-seventh day of life. Because of this finding she was given a thirty-day course of ACTH (40 mg. per day for the first two weeks, 20 mg. per day during the third week, and 15 mg. per day during the final week). However, during the third week of ACTH therapy she became edematous and developed bronchopneumonia. *Ps. aeruginosa* was cultured from the throat and nasopharynx and later from the blood. Multiple abscesses, from which the microorganism was cultured, appeared on the buttocks. Chloromycetin and penicillin were ineffective. ACTH was discontinued at the onset of her terminal illness. The infant died on her ninety-fourth day of life.

Post-mortem examination revealed, in addition to the lesions previously mentioned, multiple pulmonary abscesses and massive symmetrical porencephaly. *Ps. aeruginosa* was recovered in pure culture from the pulmonary lesion.

CASE 4.—J. L., a 1,559 gram premature female, developed stages I and II of retrolental fibroplasia at 3½ weeks of age. She was placed on a thirty-day course of ACTH identical in dosage to Case 3. Three days before the final dose of ACTH was given, she developed bronchopneumonia, and the throat culture, which had revealed *Ps. aeruginosa* in small numbers before ACTH was started, now showed innumerable colonies of this microorganism. Chloromycetin was ineffective and the infant died twenty-four hours after the onset of her pneumonia. Post-mortem examination confirmed the presence of bronchopneumonia; *Ps. aeruginosa* together with a coagulase-negative staphylococcus were isolated from the pneumonic lesion.

CASE 5.—L. L. B., a 1,049 gram male premature infant, developed respira-

tory distress and cyanosis on the fifth day of life; cultures of blood, pharynx, and nasopharynx taken at onset of distress revealed the presence of *Ps. aeruginosa*. Chloromycetin was given for the next twelve days. On the seventh day of life, ulcers, from which the microorganism was cultured, appeared on the lower gingiva and sides of the tongue. Watery stools, harboring *Ps. aeruginosa*, were noted during the ensuing ten days. The oral lesions healed completely and within three weeks the infant appeared clinically well. *Ps. aeruginosa*, however, was still present in the throat, nasopharynx, feces, and on the skin.

At 6 weeks of age, because of beginning retrolental fibroplasia, ACTH was started in the same dosage schedule as in Cases 3 and 4. Concomitantly, Aureomycin was given for nine days. On the twentieth day of ACTH therapy, the infant's temperature rose to 101° F., edema of the trunk increased, loose stools, which had been noted only sporadically during ACTH therapy, became constant. ACTH was discontinued. Chloromycetin was given, and two weeks later the infant was well with the exception of bilateral detachment of the retina.

There can be little doubt that *Ps. aeruginosa* contributed significantly to the illness of these five patients. It is interesting to note that the infection followed the administration of ACTH in two of the fatal cases. In the infant who recovered, two attacks of *Ps. aeruginosa* infection were observed, the first one prior to, and the second one concomitant with, ACTH therapy. No definitive statement can be made as to whether the development of the infection was facilitated by the administration of this hormone, although this possibility has to be considered seriously. It should be pointed out that ACTH was administered to twenty infants during the observation period when *Ps. aeruginosa* was prevalent in the nursery. Antibiotics (Aureomycin, Terramycin, Chloromycetin, streptomycin, penicillin, alone or in combinations of two or three) were administered concurrently to sixteen of these twenty infants. *Ps. aeruginosa* was demonstrated in eleven of these infants, and yet a serious infection did not develop. In addition to the above-mentioned infections developing during or following ACTH therapy, there were also one case of severe staphylococcal sepsis and one case of thrush in infants receiving this hormone. Although there is ample experimental and clinical evidence that administration of ACTH or cortisone may increase the susceptibility of animals and human beings to infection, it is obvious that in clinical practice infection does not frequently complicate hormone therapy. The precise conditions which determine whether hormone treatment will be complicated by infection are not fully understood, and it is clear from the above observations that infection does not necessarily follow therapy even in premature infants who are carriers of potentially pathogenic microorganisms, such as *Ps. aeruginosa*.

DISCUSSION

The present study on the occurrence of *Ps. aeruginosa* in premature infants indicates that this microorganism was readily acquired, in spite of the usual precautions taken for the prevention of cross-infection. Infants exposed to this bacterial species harbored this microorganism in the upper respiratory and lower digestive tracts as well as on the skin. Furthermore, in the nasopharynx, throat, and rectum, the microorganism tended to persist for two weeks and, in some cases, much longer. The obvious transmission to many infants of this bacterial species, once introduced into the nursery, represents an extraordinary experience, since it is generally recognized that this microorganism does not belong to the regular and permanent resident bacterial flora of healthy infants and children. For example, in a study of

the flora of the nose and nasopharynx of fifty children, this microorganism was not encountered in a single case.[9] The feces of fifty healthy infants under one year of age harbored *Ps. aeruginosa* in only four instances.[10] In a thorough study on the bacterial flora of the throat and rectum of 385 infants in two maternity units, McFarlan and associates[11] apparently did not encounter *Ps. aeruginosa;* at least this bacterial species is not mentioned among the several species of bacteria which were isolated. Since this investigation was undertaken in an effort to elucidate the etiology of infantile diarrhea, it is likely that such data would have been included, had *Ps. aeruginosa* been encountered in many of these infants. This microorganism was isolated from only thirteen out of approximately 3,000 fecal specimens obtained from patients with typhoid fever, dysentery, or asiatic cholera, and in five of these thirteen patients evidence was presented that this bacterial species had caused secondary infection associated with a significant rise in homologous antibodies.[12]

The presence of *Ps. aeruginosa,* sometimes in large numbers, in the feces of premature infants free of infection and particularly of diarrheal disease illustrates the diagnostic difficulties encountered in the interpretation of such a finding in children with diarrheal disease. *Ps. aeruginosa* has been incriminated as causative agent of enteritis of children. For example, Ensign and Hunter[13] reported on an outbreak of diarrhea in a newborn nursery and presented evidence to the effect that *Ps. aeruginosa* was the etiological agent of the disease. It is interesting to note that among thirteen normal infants five harbored this bacterial species and four of these five children became sick later; the mother of the fifth infant had diarrhea. The question presents itself in each individual case as to whether the presence of this bacterial species in the feces is causal or merely coincidental. It is obvious from the results of the present study that, had diarrheal disease been present in the premature infants harboring *Ps. aeruginosa* in the feces, the enteric disease may have been ascribed erroneously to this bacterial species, although it actually may have been due to other causes. Therefore, it would be desirable, in order to differentiate actual infection from mere carrier state, to demonstrate an antibody response of such patients. The indirect or conditioned bacterial hemagglutination test, which has been used successfully for the demonstration of antibodies against salmonellae, shigellae, and escherichiae,[14-20] appears to be of particular promise for this purpose, since it offers greater sensitivity than the conventional bacterial agglutination test. This test is based on the fact that the somatic antigen of *Ps. aeruginosa,* like the corresponding antigens of other enterobacteriaceae, are adsorbed readily by red blood cells and render these modified red blood cells specifically agglutinable by homologous bacterial antibodies. Gaines and Landy[21] have demonstrated the presence of *Ps. aeruginosa* hemagglutinins, in the absence of bacterial agglutinins, in random human sera, indicating that man may come in contact with, and develop immunological response to, *Ps. aeruginosa* more frequently than has been appreciated heretofore. Whether such an exposure produces clinical manifestations in a moot question.

If, in the future, outbreaks of infantile diarrheal disease associated with *Ps. aeruginosa* should be observed, a study on the presence of this microorganism in the upper respiratory tract should be undertaken. The present data make it likely that this bacterial species may be demonstrated in the throat and/or nasopharynx. Such an investigation may shed further light on the possible transmission of enteric pathogens from the respiratory tract of patients, as it has been reported from this laboratory that salmonellae, *Shigella sonnei*, and *Escherichia coli* serogroups 111, 55, and 26 may be present in the throat and/or nasopharynx of children with diarrheal disease.

Since *Ps. aeruginosa* is not an antigenically homogenous bacterial species, the question arises as to the possible relationship between different serological types and potential pathogenicity. For many years, the role of *Esch. coli* as etiological agent of epidemic and sporadic diarrheal disease of infants has remained obscure, until data became available on the serology of this species,[22] the occurrence of but a few of the numerous serogroups in infantile diarrhea (which are but rarely found in healthy children and adults),[23] and the results of feeding studies.[24, 25] It would be interesting to learn whether certain serotypes[26] or phagetypes[27] of *Ps. aeruginosa* are associated with outbreaks of infection, such as the one reported by Ensign and Hunter,[13] and whether other types may be present in the absence of a high morbidity rate, as was the case in the present series of premature infants.

SUMMARY

A systematic investigation on the presence of *Ps. aeruginosa* in the nasopharynx, throat, feces, and on the skin of 143 premature infants was carried out and the following observations were made.

1. *Ps. aeruginosa* was isolated from the skin in 25 per cent of these patients, from the feces in 51 per cent, from the nasopharynx in 27 per cent, and from the throat in 40 per cent.

2. *Ps. aeruginosa* was found in only one individual on the day of admission in the feces, though not in the throat, nasopharynx, or on the skin; from 16 per cent to 47 per cent (depending upon the specimen) of the infants harbored this microorganism on the third or fourth day after admission, indicating that this microorganism was acquired readily within a few days after admission to the nursery.

3. Of thirty-five premature infants more than half carried this microorganism in the feces and throat for two weeks; the carrier state of the skin tended to be more transient.

4. *Ps. aeruginosa* was present in large numbers on the skin of 6 per cent of the infants, in the feces in 17 per cent, in the nasopharynx in 16 per cent, and in the throat in 21 per cent.

5. In the majority of these premature infants the presence of this microorganism was not associated with clinical infection. Systemic infection, however, occurred in five patients, four of whom died. A brief résumé of these cases is presented.

6. ACTH was administered to twenty infants for the treatment of retrolental fibroplasia, sixteen of whom also received antibiotics. Systemic infection with *Ps. aeruginosa* followed ACTH therapy in three instances.

7. The "outbreak" of the *Ps. aeruginosa* carrier state terminated without special measures, and this microor-

ganism has been encountered in premature infants during the ensuing two years only occasionally.

8. The significance of these findings, with particular reference to the *Ps. aeruginosa* carrier state and the potential pathogenicity of this bacterial species, is discussed.

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EXTRAMEDULLARY SPINAL TUBERCULOMA

A Report of a Case With Unusual Clinical and Laboratory Findings

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With the modern forms of treatment of tuberculous meningitis, cures and near-cures are becoming much more common although severe neurological deficits are present all too frequently. Similar to acute bacterial meningitis, sometimes complications arise to form a clinically and pathologically recognized entity such as postmeningitis subdural effusions. The purpose of this report is to present a case of treated tuberculous meningitis with an extremely high cerebrospinal fluid protein. The patient, while undergoing treatment for tuberculous meningitis, developed a paraplegia which cleared only to recur approximately eighteen months later, at which time an intradural extramedullary spinal tuberculoma was removed. At the present time, the patient is in a chronic disease hospital, and is now undergoing intensive physiotherapy and is able to walk with crutches and can lift the left leg sufficiently to climb stairs.

CASE REPORT

RF U-24287, a 13-year-old white male, was admitted to the contagious disease department of Cleveland City Hospital on May 4, 1951. The present illness consisted of a thirteen-day history of progressive headaches, fever, malaise, anorexia, and vomiting. Fluoroscopy of the chest at another hospital one week prior to admission had been suggestive of tuberculosis, and it was thought that he had a pleural effusion at that time. Lumbar puncture at this same hospital on the day prior to admission prompted the referal to Cleveland City Hospital as a tuberculous meningitis suspect. By the time of his admission to this hospital, he had developed the additional symptom of severe neck pain.

Further history as to the possible source of contact revealed that the brother of the patient's "girl friend" was in the contagious disease hospital with tuberculosis. The patient had gone to a special school because of reading difficulties and was said to be retarded in school.

Physical examination revealed blood pressure 124/78; pulse 64; respirations 18, and temperature 37.7° C. The patient was a pale, "slightly acutely and chronically ill individual." Examination of the chest revealed decreased breath sounds and dullness to percussion over the right lower and middle lobes and extending to the right axilla. The right lung base posteriorly also showed decreased breath sounds and increased dullness.

Neurological examination revealed a stiff neck with marked resistance to anterior flexion (the patient was careful when he moved his head), positive Kernig sign bilaterally, and a lumbar puncture initial pressure of 240 mm. of water. There was a free flow of slightly turbid fluid which contained 550 cells which were all large and small mononuclear leukocytes. The smear was negative for pyogens and acid-fast bacilli. The cerebrospinal fluid sugar was less than 30 mg. per cent and chlorides were 94 meq. per liter.

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Chest films on May 5, 1951, revealed "pleural thickening and/or effusion on the right" (Figs. 1 and 2).

Course in the Hospital.—On May 5, 1951, the patient was started on aqueous penicillin, 100,000 U. every two hours intramuscularly; sulfadiazine, 4 Gm. Stat. and 1 Gm. every four hours; and Chloromycetin, 500 mg., orally or rectally every six hours. On May 6, the tuberculin test was negative. Except for this, the evidence was good for tuberculous meningitis. A repeat lumbar puncture on May 7 revealed slightly xanthrochromic turbulent fluid containing 406 white blood cells, 96 per cent monocytes, 4 per cent polymorphonuclears. An India ink preparation was negative for torula. Cerebrospinal fluid chemistries revealed protein 900 mg. per cent; sugar 32 mg. per cent; chloride 105.3 meq. per liter. Cultures were obtained for acid-fast, torula, and pyogenic pathogens. A positive culture of *Mycobacterium tuberculosis* was obtained on May 7, with all subsequent cultures proving to be negative.

On May 8, the patient was semicomatose and incontinent. No. 1 was negative. The patient was started on treatment for tuberculous meningitis with streptomycin 0.5 Gm. every eight hours; intrathecal streptomycin 100 mg. every day for 40 days; Promizole 1 Gm. every four hours; PAS 4 Gm. every day (1 Gm. q.i.d.). The sulfadiazine and Chloromycetin were then discontinued and penicillin was changed to PPA 300,000 U. b.i.d.

On May 10, 1951, PPD No. 2 was definitely positive and by May 12 it was markedly positive. At this time, the patient became more lethargic,

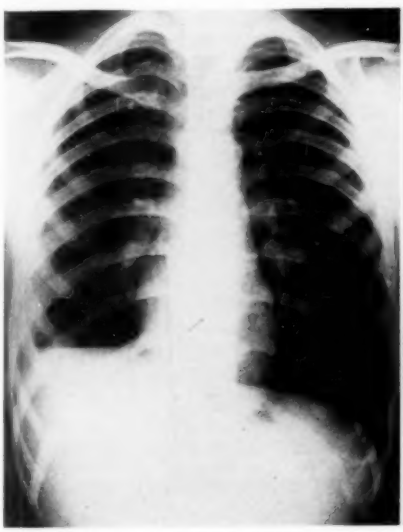

Fig. 1.

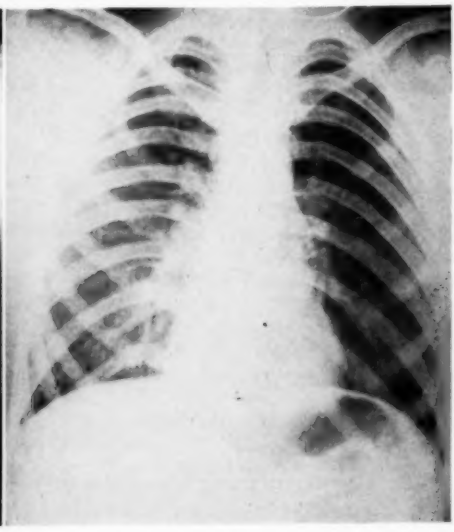

Fig. 2.

Fig. 1.—Posteroanterior view of chest (May 5, 1951) shows flattening of right leaf of diaphragm with obscuration of the right costophrenic angle consistent with pleural effusion and/or thickening.

Fig. 2.—Posteroanterior view of the chest (March 29, 1954) shows no evidence of infiltration in the lungs. The slight hazziness of the lower two-thirds of the right hemithorax may be related to pleural changes. The right costophrenic is now clear.

and developed a questionable left facial palsy, hypothermia of 34.2° C., and a question of early bulbar palsy. Because of fluctuations in the blood pressure, an Addisonian crisis was also considered. He rallied and again became alert at times.

A summary on June 30, 1951, after fifty-eight days of treatment revealed that the forty injections of intrathecal streptomycin had been completed and the patient was on intramuscular streptomycin, PAS, and Promizole, but he was not regarded as doing well. The cerebrospinal fluid protein had climbed steadily, and the patient was frequently nauseated by the PAS. At this time, he was getting monthly lumbar punctures for chemistries, culture, and cell count. A summary of the cerebrospinal chemistries is as follows (Fig. 3):

1. Started on penicillin 100,000 U. every two hours intramuscularly; sulfadiazine 4 Gm. Stat., 1 Gm. every four hours; Chloromycetin 500 mg. every six hours.

2. Culture of this fluid, positive for *Myco. tuberculosis.*

3. Semicomatose, incontinent. Started on streptomycin 0.5 Gm. every eight hours intramuscularly; intrathecal streptomycin 100 mg. every day for 40 days; Promizole 1 Gm. every four hours; PAS 4 Gm. every day. Sulfadiazine and Chloromycetin stopped, penicillin changed to PPA 300,000 u. b.i.d.

4. PPD No. 2 positive.

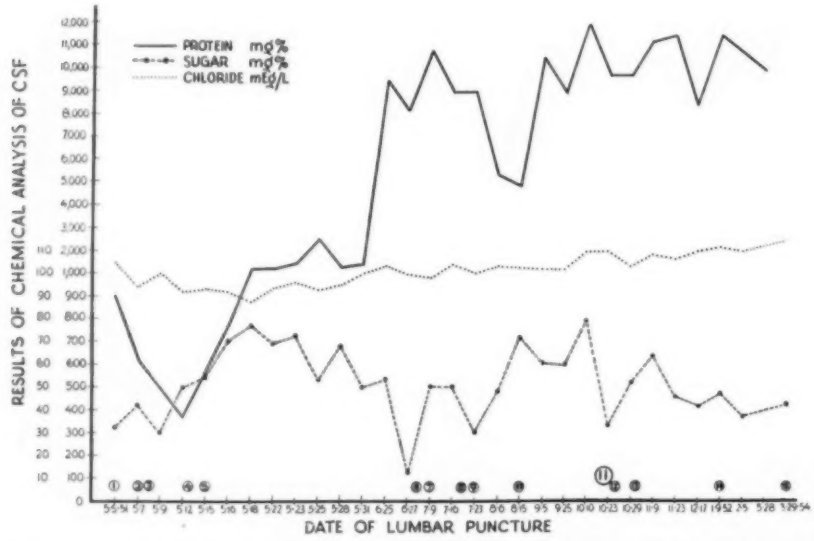

Fig. 3.—Chemical changes in cerebrospinal fluid in relation to changes in the course of the illness.

5. Marked lethargy, hypothermia, question of left facial weakness.

6. Intrathecal streptomycin discontinued (forty injections). Nauseated with PAS.

7. Intrathecal streptokinase 10,000 U. and streptodornase 5,500 U. started every two days.

8. Intrathecal streptokinase and streptodornase discontinued.

9. Intrathecal streptomycin 100 mg. daily begun (twenty-day course).

10. Second course of intrathecal streptomycin discontinued.

11. Second course of intrathecal streptokinase and streptodornase begun (Oct.

15, 1951). *Urinary retention and paresis of both lower extremities* (Oct. 22, 1951).

12. Second course of streptokinase and streptodornase discontinued (eight doses) (Oct. 31, 1951).

13. Regained control of bladder and legs.

14. Transferred to chronic disease hospital. Paraparesis present. Motor and sensory loss noted.

15. Readmission to Cleveland City Hospital.

The patient complained of temporal field blindness in the right eye on July 8, 1951. The visual fields revealed a limitation of vision in the extreme right temporal field. The fundi were regarded as normal. The cerebrospinal fluid protein value at this time was 10,800 mg. per cent. For this reason, intrathecal therapy with streptokinase and streptodornase was started on July 9, 1951 (10,000 U. SK in 2 c.c. of normal saline very two days).

On July 11, the patient felt much better, but his memory was noted to be failing. The next day he was confused and disoriented. On July 13, the patient began to have visual and auditory hallucinations.

On July 21, the patient complained of temporal field blindness, and visual fields revealed a 50 per cent temporal field with impaired vision. The cerebrospinal fluid chemistries at this time revealed protein: 9,000 mg. per cent; sugar 30 mg. per cent; chlorides 100 meq. per liter. On the possibility that the streptokinase and sterptodornase had broken down some adhesion pockets, liberating organisms into the cerebrospinal fluid and accounting for the lowering of the cerebrospinal fluid sugar, intrathecal streptomycin was again started for a course of twenty injections.

On August 15, the second course of streptomycin was completed and a marked improvement was noted during the last week of treatment. The cerebrospinal fluid protein was down to 4,800 mg. per cent as contrasted to 10,000 mg. per cent in July. There was noted a loss of vision in the temporal field on the right and, on funduscopic examination, the disc appeared slightly pale in the temporal margins.

By September 28, the cerebrospinal fluid protein was again ranging from between 10,500 and 9,000 mg. per cent. On October 13, a second course of streptokinase and streptodornase intrathecally was started every other day for intended ten doses and intrathecal streptomycin was begun every day for twenty doses. *However, on October 22, the patient developed urinary retention associated with a paresis of both lower extremities and considerable pain in his back.*

Neurological examination on October 24 revealed hyperesthesia up to one inch above the umbilicus. The right cremasteric reflex was present, whereas the left cremasteric reflex was doubtful. Examination of the legs revealed the tonus to be grossly reduced and the right leg was weaker than the left. Deep tendon reflexes were equal and active, but bilateral positive Babinski signs were present. There was some hypesthesia distally and even an anesthesia between the first and second toes bilaterally. The impression was that there was upper and lower motor neuron involvement. The intrathecal medications were discontinued and on October 27, the patient had regained control of his bladder, and the strength in his legs had returned to previous strength. However, it was noted on November 3 that bilateral leg casts were made because of contractures of both lower extremities secondary to the paraplegia, which was attributed to the streptokinase and streptodornase. On November 23, a note was made that the patient was trying to walk by pushing a wheelchair.

On Jan. 9, 1952, a transfer physical examination was made, which revealed the patient to be cheerful, cooperative, and of less than average intelligence. Examination of the eyes revealed bilateral temporal pallor of the discs, with a visual field

defect in the temporal and inferior nasal quadrant on the left, and, on the right, the visual field was noted to be quite small. There was no Kernig or Brudzinski sign. It was noted at this time that there was a decreased sensation of all modalities below L-1, no sensation below the mid-thigh except bilaterally in the right calf and knee, and posteriorly in the left calf and knee. There was no vibratory or position sense in either foot. The hypesthesia from L-1 downward included the perianal region. Patella and ankle clonus were present. Tight hamstrings were noted bilaterally with weak invertors and evertors of both feet.

In retrospect it might be wise to question a little more fully the etiology of these neurological deficits which, if more extensive examinations had been performed, might have led to an earlier diagnosis of the much later proved tuberculoma.

On Jan. 14, 1954, the patient was found to be crying in bed, complaining that his right side hurt him. The tenderness was most marked in the right lower quadrant and right flank. There was a question of rebound tenderness in the right lower quadrant. There was also tenderness in the left lower aspect of the abdomen. This was considered to be either acute appendicitis, tuberculous peritonitis, or right pyelonephritis. The patient continued to be observed and no operation was performed. The patient was transferred to a convalescent hospital, where he was placed on Promizole, 6 Gm. per day from Feb. 5, 1952, until his discharge to his mother on June 19, 1952. While in this hospital, psychological reports revealed that the patient was a boy of potentially dull normal intelligence whose intellectual development had been grossly inhibited by emotional problems, probably centering around his illness, his father's leaving, and his mother's protective attitude.

He was transferred to a training school in Pennsylvania on June 20, 1952, with a partial paralysis of both lower extremities. At this training school, he regained the use of his legs and was able to engage in sports such as soccer.

About the first week in January, 1954, the patient complained of difficulty in the use of his right leg. His gait became awkward with a marked tendency to swing the right leg. Neurological examination at that time revealed exaggerated reflexes in the right arm. In the right lower extremity, there was dragging of the leg with some spasticity and diminution of muscle power; straight leg raising limited to 30 degrees; Kernig sign negative; knee and ankle reflexes increased; and the Babinski sign positive. Position and pain sense were undisturbed. The left lower extremity was normal except for mildly exaggerated tendon reflexes and questionable Babinski sign. The eye ground examination was normal. A lumbar puncture at this time showed fluid under normal pressure but xanthochromic in appearance. The cell count was 44 and a strong four plus Pandy was obtained. Guinea pig inoculation and culture were negative for tuberculosis. A lumbar puncture was repeated in an attempt to proceed with a pneumoencephalogram, and it is noted that after about 10 c.c. of air had been injected there was excruciating pain about the level of the ninth to eleventh thoracic vertebrae, which was interpreted as "pathology of the subarachnoid type." The patient's condition deteriorated with loss of function of the right leg, increased weakness, but without loss of position sense, and another lumbar puncture was done on Jan. 25, 1954, in a repeat attempt to do a pneumoencephalogram. Again this revealed pain in the lower dorsal area. A neurosurgeon at this time believed that there were two conditions present: (1) recurrence of the old tuberculous meningitis, and (2) "subarachnoiditis" at about the level of the ninth to the tenth thoracic vertebrae.

The patient's condition continued to deteriorate, and the neurosurgical consultant reported the positive neurological findings were cerebellar ataxia, pendular reflexes; right spastic involvement; spinal defect of tenth to eleventh vertebrae; tenderness to percussion of eleventh thoracic vertebra. The diagnosis was made of obstructive subarachnoiditis at the level of the eleventh thoracic vertebra and possible tuberculoma of the left cerebellar hemisphere.

The process progressed until the patient was unable to walk, when he was flown back to Cleveland on March 27, 1954. At that time, a supplementary history revealed that the patient had begun to have some mass reflexes in his lower extremities, and, for two weeks prior to his second admission, the patient had lost control of both his bowel and bladder. The patient stated that injection of air into the subarachnoid space had caused severe pain in the back and abdomen at the lowermost thoracic region. The pain was located anteriorly just below the costal margin. A similar but less severe pain persisted from that time until his admission, being aggravated by lying flat when it was almost constant; or sitting in bed when it was intermittent.

At this time physical examination revealed the blood pressure to be 128/80, temperature 37.5° C., pulse 112, respiration 24. The patient was a well-developed, well-nourished white male who appeared neither acutely nor chronically ill. He was oriented and answered questions readily. Although possibly not of average intelligence for his age, he certainly was not markedly subnormal and was evidently well adjusted to his illness.

Neurological examination revealed very slight horizontal nystagmus bilaterally, but no cerebellar signs or symptoms and no papilledema; marked nuchal rigidity; complete paralysis of both lower extremities with increase in muscle tone and bilateral mass reflexes; sensory loss to all modalities to T-9 on the right and T-10 and T-11 on the left.

X-rays of the chest, skull, and complete spine were normal (Fig. 2). On March 29, 1954, a myelogram was performed, at which time the lumbar puncture revealed a slow flow of xanthochromic spinal fluid and a complete block to Queckenstedt's test. The initial pressure was 20 mm. of water. A cell count revealed 44 white blood cells and a four plus Pandy. The cerebrospinal fluid chemistries on this fluid revealed the protein to be 5,385 mg. per cent; sugar 51 mg. per cent; chlorides 114.8 meq. per liter. Culture was negative for acid-fast bacilli. The

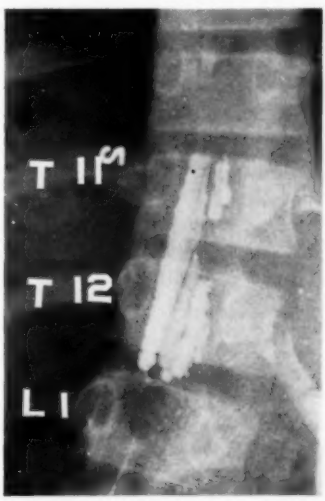

Fig. 4.—Myelography in the posteroanterior view shows a sharp complete block at the level of the upper border of the eleventh thoracic vertebra.

myelogram revealed a complete blockage of the subarachnoid space at the level of the superior border of the body of T-11 (Fig. 4). The study failed to reveal the nature of the block, but presented a sharp, well-defined border.

A neurological consultant believed that there was residual and possible reactivation of the tuberculous men-

ingitis with constrictive pachymeningitis, meningoencephalitis, and meningomyelitis.

With the preoperative diagnosis resting between tuberculous arachnoiditis with or without tuberculous abscess or tuberculoma, a complete laminectomy was carried out on March 31, 1954, from T-6 to L-1, and a spinal arachnoiditis was found which extended from the lower end of the exposed dura to T-6, where for the first time a clear, colorless spinal fluid was obtained. At the level of T-9-10, a well-circumscribed tuberculoma was found which lay inside of the dura, but outside of the arachnoid, and compressed the spinal cord to the left of the midline (Fig. 5). This tumor mass was removed by sharp and blunt dissection and seemed to have a small extension which appeared to go out the nerve root sleeve at T-9-10 interspace. The

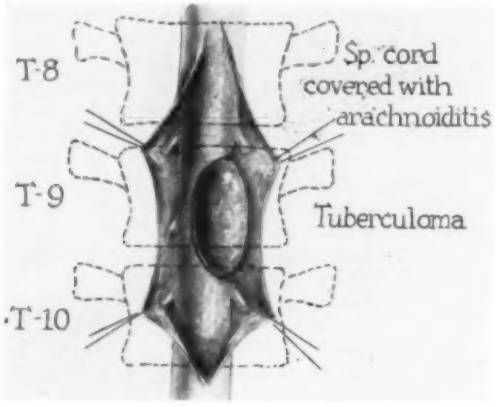

Fig. 5.—Schematic drawing of operative findings in relation to vertebral level. (Note: Defect shows difference between level of myelographic defect and level of tuberculoma, as shown in Fig. 4.)

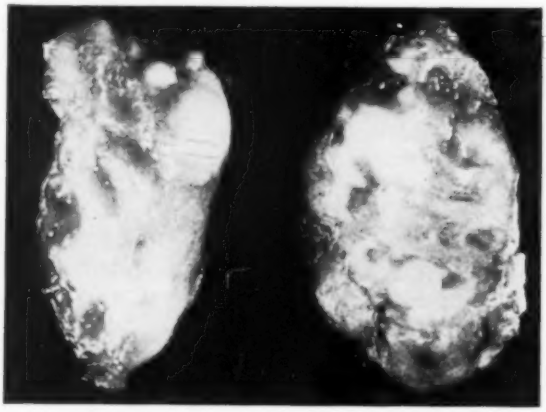

Fig. 6.—Operative specimen split in two halves showing the well-circumscribed tuberculoma and fibrocaseous contents. Specimen measured 2 x 1 x 1 cm.

dura was left open and the wound was closed in layers.

A direct smear of the purulent material obtained at the time of operation was positive for acid-fast bacilli. Pathological report of the tuberculoma was fibrocaseous tuberculosis (Fig. 6).

Postoperatively, the patient had an uneventful course except for severe transient hyperesthesia over the abdomen. He seemed to have some return of pain sensation over the right foot in a patchy fashion about the second postoperative week, as well as a fairly good return of pain sensation in the gluteal region. He still had some mass reflexes in the lower extremities. After consultation with a pediatrician, the patient was prophylactically placed on streptomycin, PAS, and isoniazid. The patient was to be maintained on PAS, and was transferred to a chronic disease hospital to undergo intensive physiotherapy. At this hospital, the patient has now regained the power to walk with braces and crutches. He has had sufficient return of motor power in the left lower extremity to enable him to walk up and down stairs. Sensory return is patchy. His course has been complicated with repeated bouts of urinary infection and, on one instance, bladder calculi had to be removed inasmuch as sphincter control has not returned to the bladder, although he is having good control of his bowels.

DISCUSSION

Bucy,[1] in a discussion of intradural spinal granulomas, presented a case which is very similar to this one. His patient has subsequently (1954) developed further extension of his pathological process and is now paraplegic.[2]

This case is presented because of the belief that with increasing numbers of patients who are cured of tuberculous meningitis, more and wider varieties of complications are going to be seen associated with this disease process. In this case, it might have been possible to have diagnosed the ultimately proved tuberculoma two years prior to its removal. It was also decided to present this case as a well-documented one, in which the spinal fluid protein, over the course of three years, was found to be extremely high, going to 12,000 mg. per cent on one occasion.

SUMMARY

Presentation is made of a case of treated bacteriologically proved tuberculous meningitis complicated by an intradural extramedullary spinal tuberculoma. This case was associated with a very high cerebrospinal fluid protein throughout the course of the disease.

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CHLORPROMAZINE,* A USEFUL ANTIEMETIC IN PEDIATRIC PRACTICE

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THE distressing frequency of vomiting associated with numerous conditions in pediatric practice is well known. Causes *unrelated* to obstructive alimentary tract disease are common. We have been agreeably surprised to find that chlorpromazine is a useful drug in abolishing the symptom in many cases.

Its mode of action appears to be central.[1, 2] The findings presented herein represent results of close clinical observation without paired controls. Past experience with numerous home remedies invoked by parents, belladonna-containing compounds, barbiturates, soda fountain cola syrups, and an allied phosphorated carbohydrate solution available pharmaceutically, have given extremely variable results as compared with the striking results with chlorpromazine. Ample opportunity to make a clinical evaluation was afforded in our outpatient section approximating 50,000 annual visits in pediatrics, and on the wards.

DISEASES FOR WHICH EMPLOYED

Our largest experience has been with infants and children whose vomiting was associated with undifferentiated acute respiratory disease, an epidemic of nausea and vomiting syndrome of unknown etiology (a late spring and summer outbreak occurred in 1954) and in acute otitis media. Our next largest experience has been with milder degrees of regurgitation in young infants associated with faulty maternal technique of feeding. Smaller groups and individual cases of vomiting in children with poliomyelitis, tuberculous meningitis, pulmonary tuberculosis, communicating hydrocephalus, congestive heart failure, bronchial asthma, mumps pancreatitis, and generalized collagen disorder associated with the acute aseptic meningitis syndrome have all been treated. Ninety children have been treated thus far. An astonishing array of unrelated clinical conditions associated with vomiting in adults has been successfully managed with this drug.[3, 4, 5]

METHOD OF ADMINISTRATION AND DOSAGE

The customary daily dosage approximated 2 mg. per pound per day in four equally divided doses. Oral administration was preferred when feasible, using the 10 and 25 mg. tablets. Not infrequently the dose was vomited, only to be repeated, following which it was generally retained. Its effectiveness in a given child could generally be determined within eight to twelve hours. Following the observation that if the drug was then withdrawn the vomiting resumed in the ensuing twelve hours, our practice was to continue the administration of chlorpromazine for two to three days. Chlorpromazine may be injected deeply into

From Department of Pediatrics, University of Louisville, Children's Hospital, and Louisville General Hospital.

*Thorazine (Smith, Kline & French Laboratories). We are indebted to Mr. Edwin Boone for furnishing tablets and ampouled thorazine.

the muscles with a very prompt antiemetic effect. We give half the calculated oral dose and repeat in four hours if vomiting persists; otherwise the oral route is resumed. Its effect via this route is very prompt, lending support to the view that the results are not due to primary effects in the gastrointestinal tract.

SIDE EFFECTS

The only side effects observed were mild drowsiness, which, in the types of patients we were treating, was not disadvantageous and moderate abdominal distention producing very little discomfort. The former symptom occurred in as many as 25 per cent of the patients and the latter was somewhat less frequent.

It is difficult to express the results obtained with precision except to say that in the larger groups with undifferentiated acute respiratory disease, otitis media, and those with the epidemic nausea and vomiting syndrome, the results were excellent to good within eight to twelve hours in 75 per cent of the patients.

We remain aware of the danger of symptomatic treatment but believe that the supression of individual symptoms need not mislead one with respect to diagnosis or proper management of the underlying condition.

SUMMARY

Chlorpromazine has been used in clinical pediatric practice for a wide variety of nonalimentary conditions associated with vomiting. It has given surprisingly favorable symptomatic results in 75 per cent of the ninety infants and children so treated. A mildly sedative side effect was noted. In our clinical experience it appears to be the first agent generally available that has this antiemetic effect which is presumed to operate by raising the threshold of the emetic centers in the central nervous system.

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REGIONAL ENTERITIS IN CHILDREN

Report of Two Cases

William K. Howard, Captain, MC, USA, Edwin J. Pulaski, Lieutenant Colonel, MC, USA, and Robert W. Morrissey, Major, MC, USAF

THERE have been many reports on regional enteritis since it was first established as a disease entity in 1932 by Crohn and associates.[1] Only recently, however, Storrs and Hoekelman[2] called attention to the condition in children. They were able to find in the literature only twenty-eight cases of regional enteritis in children from birth to 15 years of age, and reported an additional eight cases of their own. The following two cases are presented in the hope that they may contribute to the knowledge of a disease in which the etiology is obscure and the incidence may be more common than realized.

CASE HISTORIES

Case 1.—This patient, a 2½-year-old white girl who was the product of a full-term, uncomplicated pregnancy and normal spontaneous delivery, weighed 7 pounds 12 ounces at birth. She was given Similac, then an evaporated milk formula. No feeding difficulties were encountered and orange juice and oleum percomorphum were begun at one month of age. She had had no known allergy, no serious illnesses, no contagious diseases, and no operations. Her growth and development had been normal.

Both parents and two siblings were living and in good health. One sibling had "asthmatic bronchitis."

Two and one-half days prior to admission the patient awoke feeling ill and vomited. She had been constipated and was given several enemas, but with poor results. Later, she developed intermittent abdominal pain occurring every ten to fifteen minutes. There was no fever.

The child was well developed and well nourished. She was lying with her legs drawn up on her abdomen and was moaning and crying. Her abdomen was distended and tympanitic. There was a generalized abdominal tenderness which was more pronounced in the right lower quadrant. No organs or masses were palpated. She appeared moderately dehydrated. A rectal examination was negative.

A plain roentgenogram of the abdomen demonstrated a distended loop of ileum in the subhepatic region but no distention of the colon. An exploratory laparotomy revealed the entire mesentery of the small bowel to be extensively involved with mesenteric adenitis, and some of the glands were as large as an acorn. It was felt that these glands might have embarrassed the circulation to the terminal ileum since no pulsating or palpable vessels were found in the mesentery to this segment of bowel. A seven- to eight-inch segment of ileum was enlarged and cyanotic, with adhesions of the serosal surface. This portion of the ileum was resected and an ileoileostomy performed, since a small segment of ileum near the cecum was felt to be normal.

Pathological Description.—Gross: The portion of bowel resected was purplish-red in color, thickened, and had a diameter of 2.5 cm. There were several areas of necrosis of the wall and one perforation. The purplish-red serosa was very congested and covered with a fibrinous exudate. The mucosa was granular, congested, and covered with a mucopurulent exudate.

From the Walter Reed Army Hospital, Washington, D. C.

Microscopic: There was marked thickening of the submucosa by edema, and throughout this layer there were numerous large, dilated lymphatics. There was an occasional lymphoid aggregate in the lamina propria, and all had markedly hyperplastic centers. The epithelioid cells were polygonal in shape with an abundant, granular, eosinophilic cytoplasm and somewhat prominent, hyperchromatic nuclei. In some areas, these follicles extended into and through the muscularis mucosa. The mucosa covering the follicles was markedly thinned. The muscularis and serosa contained a few acute inflammatory cells. Sections of a lymph node showed a marked lymphedema. The follicles were increased in number and size and contained centers of the same type epitheloid cells as described.

CASE 2.—This patient, a 5½-year-old white girl, was the product of a full-term, uncomplicated pregnancy and a normal spontaneous delivery. Her birth weight was 6 pounds. The neonatal period was uneventful, no feeding difficulties were encountered, and growth and development had been normal. The immunizations were complete.*

The family history was negative and both parents and one sibling were living and in good health.

In February, 1953, while in Kenya, Africa, the patient was reported to have had "hemorrhagic chicken pox" associated with blood-streaked mucus in the stools and severe abdominal pain. She was hospitalized for about one week during which time she recovered from the chicken pox but continued to have episodes of abdominal pain and distention of varying severity and duration. The episodes occurred every few days to one week apart. The pains were intermittent and were relieved spontaneously, or by applying a hot-water bottle to the abdomen. Vomiting occasionally occurred with the attacks and usually helped to relieve them. After the original episode, the stools were normal and remained so, with no change in bowel habits. Her appetite was poor and she lost weight.

She was rehospitalized and studied thoroughly. Gastrointestinal x-ray studies, barium enema, and excretory urogram were all normal. The stools were negative for ova, parasites, amebae, and pathogens. Agglutinations, Mantoux test, and a number of urinalyses were also negative.

She was given a course of Aureomycin but there was no improvement. A subsequent exploratory laparotomy revealed enlargement of mesenteric nodes, free fluid in the peritoneal cavity, and a little thickening of the colon. Further exploration of the bowel revealed no pathological changes, and an appendectomy was performed. Shortly after this, however, the symptoms returned.

A sigmoidoscopy revealed changes of chronic bacillary dysentery, although the cultures were negative. The patient was given courses of emetine, Terramycin, streptomycin, and chloramphenicol. The episodes slowly decreased in frequency and her general condition improved.

On Nov. 2, 1953, she was observed in a typical attack which lasted one and one-half hours. She was having intermittent abdominal pain and had vomited once at the onset of the attack.

The patient was well developed and well nourished. She was in moderately severe pain. Abdominal distention was present and the pattern of distended large bowel was visible on the abdominal wall. There was a generalized tenderness over the abdomen, and the liver was palpable 2 cm. below the costal margin. No other organs or masses were felt. Her hematological and urinary findings were normal, and a rectal examination was negative.

A plain roentgenogram of the abdomen demonstrated large dilated loops of the large bowel, and a lower bowel obstruction was suspected. A barium

*This patient was under the care of Patience Davies, M.B., M.R.C.P., D.C.H., Nairobi, who supplied a complete summary of the patient's course. The surgeon was Mr. Gerald Anderson, M.S., F.R.C.S., Nairobi.

enema was attempted, but the barium progressed only as far as the lower sigmoid, and by this time the symptoms had subsided. A second barium enema demonstrated some redundancy of the sigmoid and smoothing of the mucosa, suggestive of edema. A sigmoidoscopic examination to a depth of 12 cm. was negative.

An exploratory laparotomy was performed, and, upon entering the peritoneal cavity, dilated loops of jejunum were encountered. A thickened discolored segment of mid-jejunum with multiple old adhesions was removed together with the involved mesentery and lymph nodes. A jejunojejunostomy was performed. Postoperatively, the patient received antibiotics and supportive therapy and her recovery was uneventful.

Fig. 1.—Case 2. Gross specimen showing the thickening and stenosis of the bowel and an enlarged lymph node.

Approximately one month after surgery the patient was doing well and had gained weight, and gastrointestinal x-ray studies at that time were normal.

Pathological Description.—Gross: A 4 cm. segment of the removed bowel showed a thickened, injected, edematous serosa tapering off at each end into normal-appearing tissue (Fig. 1). The underlying bowel wall was thickened and indurated, producing stenosis of the lumen. There was ulceration of the mucosa near this stenotic area, with a covering of inflammatory membrane which was gray, thick, and coarsely nodular. The bowel mucosa was flattened, edematous, and finely granular.

Microscopic: A section of the specimen in one area revealed a pyogenic membrane and inflammatory cells replacing the mucosa. Beneath this, the submucosa consisted principally of granulation tissue containing a diffuse infiltrate of acute inflammatory cells, polymorphonuclear leukocytes, numerous eosinophils, lymphocytes, and plasma cells. The submucosa was markedly thickened with edema and contained numerous lymphoid aggregates, some of which formed granulomas. In some areas these formed hyperplastic growths, many of which were on the margin of the lymphatics and compressed these structures. The muscular layers were infiltrated with inflammatory cells similar to those in the submucosa. The serosal layer was markedly edematous and also contained numerous polymorphonuclear leukocytes and eosinophils. Sections of the mesentery showed marked thick-

ening with edema and infiltration with acute inflammatory cells. Numerous granulomas were also present.

The lymph nodes were made up of numerous small nodes with marked edema and fibrosis of the interstitial tissue surrounding these nodes. There was an increase in the number of follicles. The center of these was markedly hyperplastic and contained the same type of cells found in the granulomas. A few giant cells were found in the submucosa and in the lymph nodes.

DISCUSSION

In the majority of children under 15 years of age reported to have had regional enteritis, the clinical manifestations have simulated those of acute appendicitis.[2]

The diagnosis in each of these cases was made primarily by the gross appearance of the involved segment of bowel, mesentery, and lymph nodes as observed at the exploratory laparotomy. Variable gross pathological changes have been reported, ranging from free fluid, mild thickening and edema of the bowel, mesentery, and lymph nodes, to marked thickening, stenosis, adhesions, and perforation. The terminal ileum and adjacent colon have been the primary sites of pathological changes with very few cases involving other areas of the gastrointestinal tract. Abdominal pain has been a constant finding, and was frequently associated with vomiting.[2-15]

In the majority of reported cases, manifestations of the disease have subsided without specific therapy and without recurrences. Some of these patients have been followed as long as thirteen years.[2]

Histopathological lesions, characteristic of this disease, have been described by a number of authors and are evidently sufficiently established to permit the differentiation of regional enteritis from sarcoidosis, tuberculosis, Strongyloides infestation, and nonspecific ulcerative colitis. However, the etiology still remains obscure.[16-19]

Both cases reported here are somewhat unusual. Case 1 presented as an acute small bowel obstruction and is thought to be one of the earliest acute cases reported in children. Case 2 presented as a chronic partial lower bowel obstruction and is one of the few cases reported in children which ran a chronic clinical course and in which the jejunum was involved.

The findings reported at the first exploration of Case 2 are compatible with a diagnosis of early acute regional enteritis. The lesion in the jejunum may have been present at that time, but the changes were so minor that they went unnoticed. This case is more typical of the clinical course of the disease as observed in the adult, that is, multiple areas of involvement, persistently recurring symptoms, and progressive changes leading to complications.[1, 20]

Treatment in both cases was in accordance with the principles outlined by a number of authors.[21, 22] A trial on a medical regime of observation, antibiotics, and supportive therapy would seem warranted in all cases of regional enteritis in children, except in those with complications, because an acute, mild, spontaneously subsiding clinical course is the rule in children. Failure of the medical regime or the development of complications would call for surgical intervention. The use of hormones has proved to be of temporary benefit only and

has been reported to mask the progress of the disease.[23, 24]

It should be pointed out that the diagnosis was not suspected in either of these patients prior to operation. The frequency with which the disease occurs in the acute form should be emphasized, and the condition should be considered in all cases of unexplained abdominal pain in children.

Follow-up of this condition in children should extend through the 20- to 40-year age period, since this is the age range when the disease is more commonly observed.[1, 17, 20] Perhaps it is premature to suggest that acute regional enteritis in children is a separate entity as proposed by Storrs and Hoekelman[2] and Bargan.[25]

SUMMARY

Two cases of regional enteritis in children are presented—one acute, with complications, and one chronic, with complications.

The clinical course of regional enteritis in children is more often the acute form, simulating acute appendicitis and subsiding spontaneously.

Regional enteritis should be considered in all cases of unexplained abdominal pain in children.

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TREATMENT OF ACUTE BENADRYL (DIPHENHYDRAMINE HYDROCHLORIDE) INTOXICATION WITH SEVERE CENTRAL NERVOUS SYSTEM CHANGES AND RECOVERY

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MANY cases of Benadryl (diphenhydramine hydrochloride) intoxication have been reported in children and infants, several of which terminated fatally.[1-6] The amount of Benadryl ingested varied from 100 to 500 mg. Disturbances of the central nervous system were especially common. Convulsions of the major motor (grand mal) tonic-clonic type, which were unusually difficult to control and which were often preceded by athetoid movements and muscular twitchings, were frequently observed. Sachs[7] noted drowsiness, dizziness, nervousness, and dryness of the oral cavity as the most frequently encountered reactions. Other manifestations often seen are vertigo, cerebral depression or stimulation, confusion, delirium, tremors, blurring of vision, tinnitus, hallucinations, ataxia, parathesias, respiratory depression, and stupor.[1-9] Children seem particularly prone to develop severe convulsions from Benadryl overdosage.

Benadryl intoxication may, in many instances, simulate atropine poisoning because fixed dilated pupils, flushed facies, and hyperthermia are so often observed. A careful investigation of the source of the poisoning is therefore essential in every case.

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Churchill and Gammon[13] have reported that the administration of Benadryl to some adult epileptic patients increased the abnormalities in their electroencephalograms and also, in some instances, caused clinical convulsions.

Wyngaarden and Seevers[8] produced progressive excitability, tremors, spastic jerking, and tonic-clonic convulsions in monkeys by the administration of Benadryl and Pyribenzamine (tripelennamine hydrochloride). The administration of Pentothal (thiopental sodium) in small doses controlled the convulsions in these monkeys. The postconvulsive phase required judicious use of a stimulant (caffeine) to prevent death from respiratory depression.

Patients who died of the Benadryl poisons had respiratory failure and coma which occurred from two to eighteen hours after the ingestion of the Benadryl. Autopsy findings in the reported fatal cases of Benadryl intoxication were similar to those found in patients who died of heat stroke. Anoxic changes were present in the brain, heart, liver, lungs, kidneys, and thymus. Davis and Hunt[2] noted that the cerebral hemispheres showed flattened convolutions and were increased in size. Aaron[6] believed that interalveolar or intra-alveo-

lar hemorrhagic edema of the lung was extremely suggestive of a histamine effect.

The purpose of this paper is to present the type of therapy employed in the treatment of an 18-month-old baby following the ingestion of 350 mg. of Benadryl, the child exhibiting symptoms and signs indicative of severe brain damage but subsequently recovering completely.

CASE HISTORY

D. B., an 18-month-old white female infant, was admitted to the Johns Hopkins Hospital dispensary approximately thirty minutes after the accidental ingestion of 350 mg. of Benadryl.

Her birth, mental and physical development were normal. She had had no specific illnesses, no head injuries or convulsions. There was no known history of convulsive disorders in her family.

At 10:15 A.M. on May 14, 1953, the patient swallowed seven 50 mg. capsules of Benadryl. Within the next one-half hour, while on the way to the hospital, she became irritable and "jumpy," but did not vomit. Gastric lavage was instituted immediately upon arrival. Approximately forty-five minutes after the ingestion of the Benadryl she became comotose and began to convulse. The convulsions were of the generalized tonic-clonic type. Phenobarbital (120 mg.) was given intramuscularly without effect. The temperature at this point was taken for the first time and found to be 39.5° C. (r.). After fifteen minutes of severe, generalized convulsions, endotracheal intubation was accomplished, and during the next ten minutes 50 mg. of Pentothal was given intravenously. Pentothal 37.5 mg. was again given intravenously before the convulsions, which lasted for one hour, were under control. At this point the child almost ceased to breathe and positive pressure respirations were required for a short period. By this time the temperature had risen to 40.2° C. The patient was sponged with tepid water and given 150 mg. of acetylsalicylic acid by rectum and then transferred to the pediatric ward. Physical examination on admission to the ward revealed the temperature to be 40.0° C. (r.), pulse 180, respirations 60, blood pressure 90/60. She was a well-developed, comatose infant with good color and respirations well maintained via an endotracheal tube. The skin was clear. There were a few fine râles over the left lateral chest but the lungs were otherwise clear. Heart sounds were good and no murmurs were heard. The abdomen was soft. There was no response to painful stimuli but the deep tendon reflexes were present. The extremities were otherwise flaccid. Bilateral Babinski signs were present. The pupils seemed fixed at mid-position and the optic discs were well outlined. The infant was placed in humidified oxygen. During the first three hours on the ward 50 mg. of Pentothal was given intravenously in small increments to control muscular twitching movements which occurred each time she was disturbed. Endotracheal and gastric tubes were removed after being in place for five hours.

Twenty-four hours after admission, the infant was quite dazed, but was taking milk by nipple without difficulty. She made no attempt to sit or pull up. Mild flaccid paralysis of the left arm was noted but other extremities moved freely. After about forty-eight hours it became apparent that she had cortical blindness. The optic fundi remained normal throughout her hospital stay. She responded in a playful though very infantile manner to stimulation but had no apparent recognition of her parents' voices. Hearing was thought to be impaired. She spoke no words during her hospital stay and her mental age on discharge, after one week, was estimated at six months.

Hemogram, urinalysis, and serologic test for syphilis were normal. There was no evidence of renal or hepatic damage.

Within two weeks after discharge from the hospital, the infant could vaguely follow light and was able to stand with support. She began to react to different voices and speak syllables. Within two months she could walk and run, speak single words, and was thought to have perfect vision. Six months after the Benadryl ingestion she could talk in short phrases. When the patient was 28 months of age (ten months after the ingestion of Benadryl), a psychometric evaluation placed her over-all intellectual functioning at a low normal level but it was judged that compensatory development was rapidly overcoming the toxic affects of the drug.

DISCUSSION

From a study of the cases reported to date and our experience with this case, it is possible to formulate a rational approach to the management of these patients. In the absence of a specific antidote for Benadryl, the treatment remains entirely symptomatic. Immediate attention should be given to the following aspects of treatment: (1) gastric lavage, (2) rapid termination of the convulsions, (3) careful attention to any signs of respiratory embarrassment, particularly when large doses of barbiturate are used to control the convulsions, (4) reduction of hyperthermia, and (5) supportive therapy for coma.

As with any poisoning, an attempt should be made to remove as much of the unabsorbed agent from the stomach as soon as possible. Gastric lavage with tepid water in amounts from 500 to 1,000 c.c. is usually sufficient for this purpose. The material aspirated should be examined for particles of capsules and saved for drug analysis when the diagnosis is uncertain. Milk may also be used for this purpose.

Convulsions, when caused by Benadryl intoxication, are generally severe and protracted. Since it is known that prolonged convulsions may cause permanent brain damage, it is imperative that control of the seizures be attempted as soon as possible. The short-acting barbiturates, such as Seconal (secobarbital) and Pentothal, or ether are probably the most effective agents for the control of the convulsions. We obtained an excellent result in our patient by administering an initial injection of phenobarbital, followed by subsequent intravenous injection of Pentothal. The Pentothal should be given in small doses (30 to 60 mg.) sufficient to keep the patient from convulsing. It can be repeated as often as is necessary for the control of convulsion. This drug, however, should only be given under hospital conditions where adequate means of resuscitation and oxygen therapy are readily available.

Guard[4] reported a good result with the use of Seconal. Seconal is usually administered in capsule form via the rectal route. In order to promote quicker absorption, it is advisable to make several pin-point holes in the capsule, insert it high up into the rectum and avoid inserting it in the fecal mass; otherwise, absorption will be delayed. Following this, the buttocks should be taped with adhesive to prevent expulsion of the capsule. The recommended dosage of Seconal for the treatment of such convulsions is given in Table I.

TABLE I. AVERAGE DOSE* OF SECONAL (SECOBARBITAL) TO BE ADMINISTERED RECTALLY FOR THE CONTROL OF SEVERE AND PROTRACTED CONVULSIONS

AGE OF PATIENT (YR.)	METRIC	APOTHECARY
Under 1	50 to 100 mg.	¾ to 1½ gr.
1-2	100 to 150 mg.	1½ to 2¼ gr.
2-3	150 to 200 mg.	2¼ to 3 gr.
3-4	200 to 250 mg.	3 to 3¾ gr.
4-5	250 to 300 mg.	3¾ to 4½ gr.
Over 5	300 mg.	4½ gr.

*The conversion of the metric system of weights to the apothecary system is approximate. (From Livingston, Samuel: The Diagnosis and Treatment of Convulsive Disorders in Children, Springfield, Ill., 1954, Charles C Thomas, Publisher.)

Extreme caution must be exercised when administering the barbiturates to patients with Benadryl intoxication. Experimental evidence indicates that barbiturates and antihistamine drugs may produce an adverse synergistic sedative effect.[10-12] When large doses of barbiturates are given, the patient should be observed carefully for marked depression of respiration. Artificial respiration should be instituted at the first signs of respiratory embarrassment. Respiratory stimulants such as caffeine, amphetamine, or ephedrine should be administered as indicated. The successful treatment of the respiratory depression in our patient necessitated the use of an endotracheal tube and artificial respiration.

The hyperthermia may be controlled by the use of tepid water or alcohol sponge. Antipyretics such as acetylsalicylic acid introduced by stomach tube or by rectum may also be used. If coma develops, it should be treated with the usual supportative therapy: oxygen, antibiotics, intravenous fluids, and blood.

There is experimental and clinical evidence which indicates that antihistamines will counteract the effect of acetylcholine in a manner similar to that of atropine. This would explain the disturbances such as fixed, dilated pupils, flushed facies, and hyperthermia which are sometimes seen in Benadryl intoxication and are almost invariably encountered in atropine poisoning. Guard's patient with Benadryl intoxication was treated successfully with Prostigmin (neostigmine), in addition to Seconal, to counteract the atropine-like symptoms. Repeated doses of Prostigmin were neccessary to control the facial flushing and dilation of pupils.

We believe that the satisfactory outcome of our case was due to strict adherence to the principles of treatment, especially the maintenance of respiration by means of the endotracheal tube, and artificial respiration.

SUMMARY

A case of Benadryl (diphenhydramine hydrochloride) intoxication is presented which manifested signs and symptoms of hyperthermia, severe convulsions, cortical blindness, and marked regression of the developmental pattern, followed by complete recovery.

Gastric lavage, reduction of hyperthermia, control of convulsions with barbiturates, and support of respiration by endotracheal tube with artificial respiration were very likely responsible for the survival of the child.

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Extracts from "Some Special Points, Relating to the Education of My Children"
Diary of Cotton Mather, dated February, 1706

I begin betimes to entertain them with delightful Stories, especially *scriptural* ones. And still conclude with some *Lesson* of Piety; bidding them to learn that *Lesson* from the *Story*.

And thus, every Day at the *Table*, I have used myself to tell a *Story* before I rise; and make the *Story* useful to the *Olive Plants about the Table*.

Betimes I try to form in the Children a Temper of *Benignity*. I putt them upon doing of Services and Kindnesses for one another, and for other Children. I applaud them, when I see them Delight in it. I upbraid all Aversion to it. I caution them exquisitely against all Revenges of Injuries. I instruct them, to return good Offices for evil Ones.

As soon as tis possible, I make the Children learn to *write*. And when they can *write*, I employ them in Writing out the most agreeable and profitable Things, that I can invent for them. In this way, I propose to fraight their minds with *excellent Things*, and have a deep Impression made upon their Minds by such Things.

I mightily endeavour it, that the Children may betimes, be acted by Principles of *Reason* and *Honour*.

I first begett in them an high Opinion of their Father's Love to them, and of his being best able to judge, what shall be good for them.

The *first Chastisement*, which I inflict for an ordinary Fault, is, to lett the Child see and hear me in an Astonishment, and hardly able to beleeve that the Child could do so *base* a Thing, but beleeving that they will never do it again.

I would never come, to give a child a *Blow;* except in Case of *Obstinacy:* or some gross Enormity.

To be chased for a while out of *my Presence*, I would make to be look'd upon, as the sorest Punishment in the Family.

The *slavish* way of *Education*, carried on with raving and kicking and scourging (in *Schools* as well as *Families*,) tis abominable; and a dreadful Judgment of God upon the World.

Tho' I find it a marvellous Advantage to have the Children strongly biased by Principles of *Reason* and *Honour*, (which, I find, Children will feel sooner than is commonly thought for:) yett I would neglect no Endeavours, to have *higher Principles* infused into them.

I therefore betimes awe them with the *Eye* of God upon them.

Heaven and *Hell*, I sett before them, as the Consequences of their Behaviour here.

THE INFLUENCE OF GROWTH PATTERN ON THE MALERUPTION OF THE MAXILLARY CUSPID TEETH

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MALPOSITION or malocclusion of units of human dentition is an important health problem. Recent surveys show that 90 per cent of all children, and, by inference, adults are afflicted with a lack of normal facial and dental arch development and its attendant maleruption, rotation, malposition, or noneruption of some teeth. This is a medical-dental problem in treatment, an oral surgical-orthodontic problem in correction, and of anthropological interest in development.

We are interested primarily in a study of the factors which cause insufficient intercuspid space in the maxilla and secondarily in the mandible, although the components of the problem cannot really be separated. When there is insufficient intercuspid space, the palatal arch length is not great enough to accommodate the incisor or cuspid teeth in normal position. These teeth rotate or tip on their axis, erupt buccally, labially, or palatally (lingually in the mandible) to the median line of the arch crest or may become impacted (Figs. 1, 2, and 3).

An examination of normal and abnormal growth patterns influencing arch development begins with examination of the dentofacial complex. According to Elsasser[3] four factors are to be considered in the maxilla: (1) relation to the cranium as a whole, (2) over-all dimensions and length of the palate, (3) relation of the dentition to the alveolar bone, (4) relation to the movable mandible. Many conditions cause variance in these factors.

Individual growth capacity is of primary consideration. The greatest increase in bicuspid dimension comes at a period of accelerated growth. Henriques[5] puts this at the age of 7 to 8 years in girls and from 8 to 9 in boys, with a decided decrease in ratios at the age of 11 to 12, the normal eruption time for these teeth. In other words, the cuspid space must be completely prepared before the eruption time (Fig. 4). As Krogman[7] states, each child has his own unique biogenetic endowment. As much as five years may differ between biological and chronological age and yet development levels may be almost identical. Sicher[11] notes that eruption of the teeth has little effect on growth but that growth seems to effect eruption considerably. Physical well-being, adequate nutrition, and freedom from debilitating or growth-retarding diseases, therefore, are important factors in normal eruption and positioning of the teeth.

Predetermination of the expected adult facial patterns may give another clue to variances from the averages. Serial x-rays are taken on a cephalometric basis during growth periods in children and are then transposed to their parental films. Hereditary familial characteristics or traits in facial

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Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—Insufficient arch length in maxilla with malposition of lateral incisor.
Fig. 2.—Rotation of anterior teeth in mandible with malposition of cuspids and lateral incisor.
Fig. 3.—Crowding of maxillary anterior teeth at eruption time.

Fig. 4.—Example of lack of growth preparation for eruption of lateral and cuspid teeth.

pattern are discernible in the composite film. The Downs-Wylie[2] analysis considers these patterns. It is possible to demonstrate that the expected growth for tooth position in a child will conform to that of one parent or the other. When endo-oral and ecto-oral dimensions are considered on a functional basis, it is noted that mesio-distal relationships in the face give the best indication of dentofacial relationships. This fact seems to prove the possibility of the lateral cephalometric x-ray approach in the interpretation of dentofacial analysis.

Nance[10] finds that by the age of 8 years clear evidence of the lack of space for the permanent successors may be obtained by an analysis of the dentofacial ratios supplemented by the Ballard-Wylie[1] nomograph. Foster[4] reports that these determinations are correct to plus or minus 2.5 per cent. X-ray (Fig. 5) presented here of the case of L. C., Negro, aged 7½ years, shows a definite lack of space for the permanent incisors which are all out of proportion to the developing jaw. His growth pattern is considerably different from his chronological age. There is no glandular background for the condition, but a history of disturbed nutritional factors during the age period of birth to 2 years of age. A similar condition is often seen in children with a history of cerebral palsy and in early-age polio.

Fig. 5.—Example of lack of space for erupting permanent incisors.

Sequence of eruption is very important. Jenkins and associates,[6] in a study of eruption of the teeth, found that normal timing of eruption in the maxilla is 6-1-2-4-5-3-7 and in the mandible 6-1-2-3-4-5-7, numbering distally from the midline or central incisor. Two factors are to be noted in the maleruption of the maxillary cuspids at this point. There is no increase in length of arch size anterior to the first molar teeth after these teeth erupt. Therefore, when there is a primary lack of development of the dental arch anterior to the first molars, which can be demonstrated by intercuspid and palatine length measurements, there must follow a rotation and malposition of the incisors with subsequent palatine or buccal eruption of the cuspid or impaction and noneruption of the tooth.

Fig. 6.—Example of drifting of teeth. Bicuspid is encroaching on cuspid space.

Segmental problems resulting from tooth drift and loss of tooth space represent a large percentage of orthodontic problems (Fig. 6). Many result from premature loss of deciduous teeth with the accompanying change in eruption timing, for often early extraction of these teeth stimulates early eruption of permanent teeth into

spaces which have not been growth-prepared. From the standpoint of the oral surgeon it is noted that there seems to be an increasing demand for the extraction of these teeth, and, rightly, health preservation should take precedence over tooth position. Even greater efforts should be expended from a public health standpoint to educate parents in the necessity of preservation of their children's deciduous teeth. A possible solution, or at least help, in the preservation of deciduous teeth is slowly developing.

Fig. 7.—Injured deciduous incisor, the cause of extensive cyst formation.

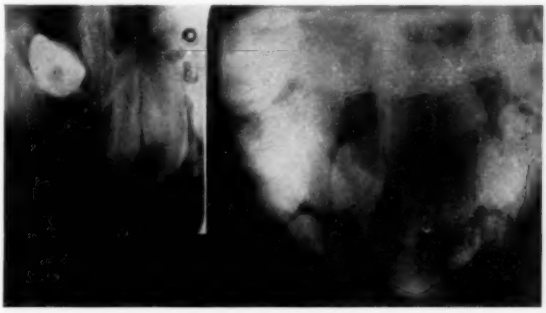

Fig. 8.—X-rays showing extensive damage to mandible by cyst.

Fig. 9.—Rotation of erupting permanent incisor due to presence of supernumerary tooth.

Various reports indicate that orthodontic anomalies due to tooth drift are 30 per cent less frequent in population areas where there is sodium fluoride to 1 p.p.m. in the communal waters. This decrease in orthodontic treatment necessity is in direct proportion to the increased retention time of deciduous teeth up to their normal exfoliation time.

When deciduous teeth are extracted before their normal exfoliation time, the permanent incisors which have erupted previously drift posteriorly, the bicuspids erupt prematurely and drift anteriorly, with the result that the cuspids are usually blocked in palatine relation from eruption. Because of articulation with the movable mandible, the drift is greater in the maxilla with more maxillary and mandibular cuspids impacted.[4]

The destruction factor of some anomalies or diseases of dentition must be considered, especially if a lack of vertical development takes place. Cleft palate, traumatic injuries, cysts, tumors, supernumerary teeth, infections, growth injuries, cerebral palsy in some instances, and polio when muscles of the face are involved, have been noted as disturbing dental growth patterns. X-rays are shown of A. D., female, aged 9 years, where a history of falling out of bed at the age of 2 and injuring the deciduous incisor is the cause of traumatic and infective cyst which has destroyed a considerable amount of bone in the maxilla, displacement and permanent damage to the permanent incisor and lateral and probably cuspid teeth (Figs. 7, 8, and 9).

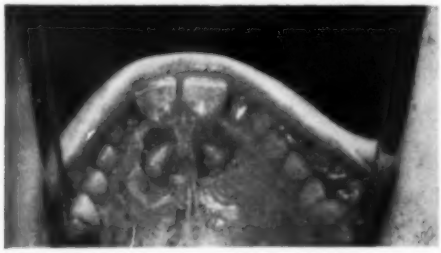

Fig. 10.—Exposure of palatally blocked maxillary cuspid teeth.

TREATMENT

Early recognition of these basic factors is the primary treatment method, stimulation of normal growth as shown needed, an adequate nutrition program, the correction of anomalies as soon as diagnosed, and orthodontic correction must be considered. Prevention of changes in eruption time is very important in treatment planning. From a surgical standpoint one procedure is to remove the deciduous cuspids after the eruption of the mandibular permanent laterals but before the eruption of the maxillary laterals. Lloyd[9] calls this the period of incisor adjustment. Occasionally the treatment must start with the extraction of the deciduous incisors if x-rays indicate the need or the permanent incisors erupt labially or lingually (palatally) to the deciduous ones. Next, the permanent first bicuspids are removed in what is termed the period of

cuspid adjustment. A third phase (Fig. 10) which may follow is the exposure of the nonerupted or blocked cuspid, excision of covering mucous membrane, and removal of overlying and impinging bone of the crown of the tooth. Packs or covering with a celluloid cap are placed to prevent the redeveloping of covering tissues. When it has been further determined how much natural eruption will take place, then the last part of the treatment is instituted, namely, orthodontic adjustment to pull the partly erupted tooth into place.[8]

CONCLUSION

Some of the factors which produce a variance in the growth pattern of the development of the maxilla with maleruption of cuspid teeth have been discussed briefly. A plan of treatment procedure for correction is presented. Early recognition of growth patterns which may produce abnormalities is important, for later surgical and orthodontic correction cannot produce the perfection of natural eruption and positioning of teeth in adequate dental arches.

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INSULIN ALLERGY

Case Report, With Response to Boiled Insulin

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ALTHOUGH insulin resistance in diabetes mellitus has been reported not infrequently, and its management is mentioned in standard medical and pediatric textbooks, a case of generalized allergy to insulin rarely is encountered. The term "insulin allergy" denotes a specifically acquired altered antigenic response to insulin protein, in contradistinction to insulin sensitivity, which denotes an altered physiologic response. Three types of insulin allergy are usually mentioned: mild local reactions, severe local reactions, and generalized reactions, i.e., severe urticaria with angioneurotic edema, circulatory failure, asthma, arthalgia, and gastrointestinal symptoms.

The incidence of generalized reactions to insulin is estimated at 1 to 1,000 cases of diabetes mellitus. Stone and associates,[1] found two cases in 2,949 patients admitted for treatment of diabetes mellitus in eight years. A special relationship between atopy and diabetes mellitus was not found by Siegal and Herzstein[2] in a study of 400 severe diabetics and 227 controls.

In the management of insulin allergy, Dolger[3, 4] suggested either rapid desensitization to insulin or a simpler method of using boiled regular or crystalline insulin, the vial of insulin being immersed in boiling water for fifteen minutes. The molecular weight of insulin being approximately equal to that of egg albumin, he stated boiling the insulin for fifteen minutes resulted in a loss of only 10 to 20 per cent of its activity, and he reported a patient with insulin allergy treated with boiled insulin who eventually tolerated unboiled insulin. Hollindar and Zinn[5] reported a case of urticaria from insulin where denaturing the insulin by boiling failed to improve the patient's condition, but, in the following case, boiling the insulin resulted in immediate disappearance of all signs of a severe generalized insulin allergy.

CASE REPORT

J. L. W., an 11-year-old white female, was admitted to Midland Memorial Hospital with diabetic acidosis, pharyngitis, and a blood sugar of 488 mg. per cent. She had a history of polydypsia, polyphagia, polyuria, and weight loss over two months, but no family history of diabetes or allergy. Within twenty-four hours her acidosis and dehydration had responded to intravenous fluids and regular insulin 25 units intravenously, stat, and 105 units given in divided doses hypodermically. The day following admission, the blood sugar was 209 mg. per cent. The urine showed only a trace of acetone, 2 + sugar, and she was taking food and liquids well by mouth. A moderately red, slightly raised, urticarial eruption with considerable itching had developed on

From the Mast Clinic.

her left arm (where the early injections of insulin had been given) approximately eighteen hours after admission. The itching improved with oral Chlor-Trimeton 4 mg. every six hours, but the rash would come and go on her thighs, buttocks, neck, arms, and body.

Approximately thirty-six hours after admission, the urine was noted to have turned a cloudy, reddish brown, very similar to that of a patient with acute glomerulonephritis. This urine specimen had a specific gravity of 1.022, a 2+ albumin, 3+ sugar, negative acetone, and was loaded with red blood cells. Her face appeared slightly puffy, but no generalized edema was noted. Blood pressure remained 98/60. Nonprotein nitrogen was 26 mg. per cent. Two days later the urine was clear, and showed only a trace of sugar. Corrected sedimentation rate was 14 mm. per hour.

She was discharged from the hospital seventy-two hours after admission on 40 units of NPH and 15 units of regular insulin at lunch and supper. Two days after discharge, she was seen in the office, feeling well, with no rash, itching, or edema. The urine was clear except for a trace of sugar, and fasting blood sugar was 109 mg. per cent. She weighed 82¼ pounds. On the following day, her mother noticed her eyelids becoming puffy and her ankles swelling. She had gained 5½ pounds (weight 87¾ pounds). Physical examination showed generalized edema of the face, eyelids, abdominal wall, arms, and 4+ edema of the ankles. The blood pressure was 96/60. She had received 60 units of NPH insulin that morning. She was put to bed, and her insulin was changed from NPH insulin to regular beef insulin, but no improvement was noted after forty-eight hours.

She was then given 20 units t.i.d. of regular beef insulin that had been boiled fifteen minutes. The next day she voided 2,500 c.c. and the following day another 2,500 c.c. The edema disappeared, and her weight dropped to 84 pounds. This boiled insulin was continued for three weeks and limited activity allowed. She had slowly gained to 87 pounds, a return to her "normal" weight, and no edema was noted. Then in addition to boiled insulin, 0.1 c.c. (4 units) of regular, unboiled beef insulin was given; in twenty-four hours she had gained 3 pounds and had developed generalized edema, not quite as severe as on the first occasion. Her urine showed no red cells, white cells, casts, or albumin, but did have a 3+ sugar. Only boiled, regular insulin was continued and she promptly lost 2 pounds in two days. Her insulin requirements by this time had dropped to regular insulin, 15-10-15.

One mouth later she developed pharyngitis, which responded well to Terramycin 500 mg. stat and 250 mg. every four hours for four days. In three weeks another bout of pharyngitis occurred. Treatment was begun with 800,000 units of fortified penicillin intramuscularly daily. She weighed 92 pounds prior to treatment. On the second day she had become edematous, and had gained 2 pounds. No rash or itching had appeared. Terramycin was substituted, and her weight returned to normal within two days. She then was admitted to the Houston Children's Hospital under the care of C. W. Daeschner, M.D., for desensitization to insulin. Following her discharge she has remained in good health taking 40 units of NPH insulin daily, and in three months has exhibited no evidence of insulin allergy.

Comment.—Fortunately, insulin resistance did not develop in this girl. Allergy to protamine or to individual species of insulin has been suggested as possible causes of insulin allergy, but, in this case, edema, urticaria, and weight gain followed the use of beef or mixed regular or crystalline insulin. It would seem that the allergy was to the insulin itself, regardless of species or preparation. Local cutaneous allergy ap-

peared within eighteen hours of the first dose of insulin. From her history, she never had received insulin previously. The local itching and urticaria were controlled by oral Chlor-Trimeton. Within five days of the onset of insulin therapy, generalized edema and a gain of 5 pounds had occurred, which did not respond to a change from pork to beef to crystalline insulin. However, within twenty-four hours of the use of boiled, regular insulin, a diuresis followed and she lost 5 pounds. She remained symptom-free on boiled regular insulin for three weeks, but again became edematous and gained 2 pounds following the use of 0.1 c.c. (4 units) of regular unboiled insulin.

SUMMARY

A case of generalized insulin allergy in an 11-year-old white girl, consisting of generalized edema, urticaria, and a weight gain of 5 pounds, responded well to the emergency treatment of boiled, regular insulin. The patient ultimately was desensitized to insulin, enabling her to take commercial NPH insulin.

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A RARE TYPE ESOPHAGEAL ANOMALY AND ITS TREATMENT

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ESOPHAGEAL anomalies are usually relieved only if considered in the category of and treated as emergency surgical conditions.

Of these anomalies, probably tracheo-esophageal fistula has received more attention from surgeons and pediatricians in the past few years than any other esophageal anomaly.

In considering tracheo-esophageal fistulas, we find they are usually classified in four types, as shown in Fig. 1.

This paper is prepared to present a fifth type of tracheo-esophageal fistula and to outline its treatment.

CASE REPORT

This 22-day-old white female infant was referred to Children's Mercy Hospital in Kansas City, Missouri, on May 29, 1953. The history revealed that this was a normal, cephalic, spontaneous, full-term delivery. The only abnormality noted after delivery was the presence of a moderately excessive amount of thick mucus from the mouth, but this was not of sufficient severity to cause concern at the time of birth. At the occasion of the first and subsequent oral feedings, the infant became cyanotic, would cough, and demonstrated evidence of respiratory difficulty. Most of the feeding in each case, however, was retained. The infant was admitted to a local hospital at 5 days of age where she remained until her admission to Children's Mercy Hospital on the twenty-second day of life.

The family history revealed that there are two siblings, one a child 4 years of age, who is living and well and in whom no anomalies are apparent. One sibling died at the age of 14 months with a history of agenesis of the bile ducts.

Physical findings at this hospital disclosed a well-developed, well-nourished female infant. The color was good and there was no cyanosis. Crepitant râles and rhonchi were heard over both lung fields. The breath sounds over the right upper lobe were diminished. Abdominal distention was prominent and there were distended veins present over the upper abdomen and the lower portion of the chest. A plastic gastric tube had been introduced before admission to this hospital and at examination this was removed. The infant was given a small amount of distilled water by mouth. This produced moderate cyanosis, coughing, and respiratory difficulty. The small amount of water, however, was retained. A gastric tube was reinserted and all subsequent feedings were given by tube.

A tentative diagnosis of tracheo-esophageal fistula was made, and, on the following day, a Lipiodol swallow was given by way of bottle and nipple. Under fluoroscopy, a fistulous tract was demonstrated with communication between the upper portion of the trachea and the esophagus (Fig. 2).

Operative Report.—The child was given fluids by indwelling feeding tube (polyethelene) and the operation was set for the afternoon of the third hospital day. Blood was available.

Under benefit of endotracheal nitrous oxide, ether, and oxygen anesthesia, and with the child in a right posterolateral thoracotomy position, a classical incision was made in the right chest, the chest being entered through the third interspace because of the underlying fistula. The pleura

From the Children's Mercy Hospital.

was clean but the right upper lobe was atelectatic and "liverlike" in color and consistency. The mediastinal pleura was incised and the esophagus and trachea exposed. Following the fistula, it was double clamped and severed between clamps. A cuff, left on the tracheal end, was trimmed and closed with three bronchial sutures of No. 000 black silk. Suction

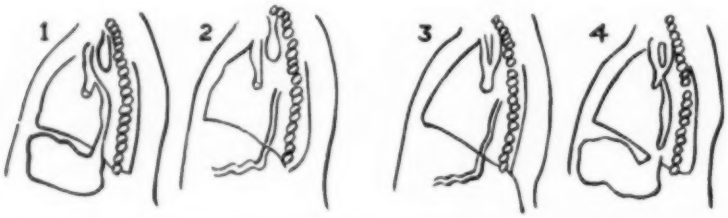
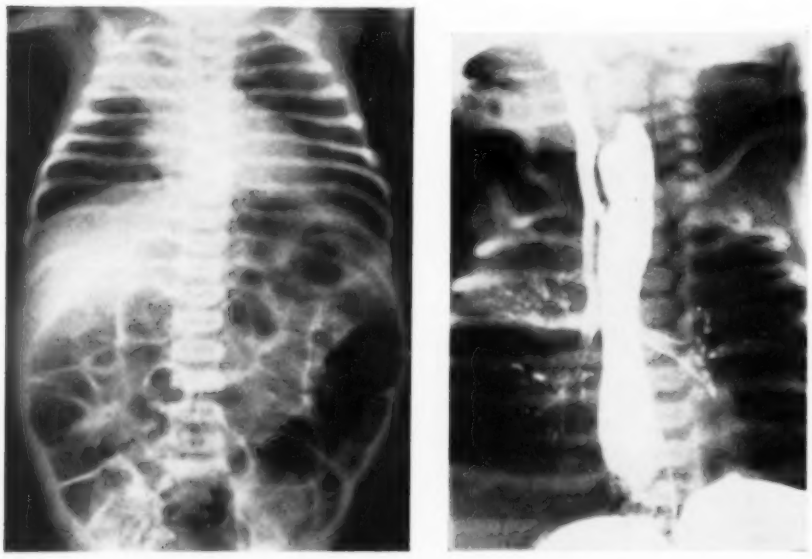


Fig. 1.—Four types of tracheo-esophageal fistulas. (Redrawn from Mitchell-Nelson Textbook of Pediatrics, ed. 6, W. B. Saunders Co.)



A. *B.*

Fig. 2.—Infant 22 days of age. *A*, Preoperative anteroposterior x-ray of chest. *B*, X-ray showing a tracheo-esophageal fistula of the H type as demonstrated with Lipiodol swallow.

ing double ligation and severance of the azygos vein, the fistula was found approximately at the level of the second rib. This measured 3 mm. in diameter, ran obliquely cephalad from the esophagus to the trachea. It entered the trachea at the cupola of the right chest. After completely freewas then applied to the endotracheal tube and the upper lobe bronchus was milked of secretions—several "plugs" being extracted. The upper lobe then filled normally. Pressure was then applied in the endotracheal tube with saline in the chest and there was no evidence of a leak. The

esophageal portion of the fistula was closed with inverting sutures of No. 000 black silk. Several sutures were used to hold the muscle over the mucosal layer. Penicillin and streptomycin were placed in the chest, and an intercostal drain was inserted in the fourth interspace and connected to an underwater seal bottle. The chest was closed in layers.

The child was placed in a Croupette for cooling purposes, and oxygen was given by nasal catheter. Feedings were given by polyethelene tube, the tip of the tube resting in the jejunum. On the fourth postoperative day, x-ray films of the chest showed a small amount of fluid in the right costophrenic angle. This was removed by thoracentesis because the intercostal tube had ceased functioning on the third postoperative day. The postoperative course was then uneventful and the feeding tube was removed on the tenth postoperative day. Oral feedings were routine and without vomiting. X-rays following Lipiodol swallow on the fourth postoperative day had revealed no evidence of a leak and no narrowing of the esophagus. The child left the hospital on the fourteenth postoperative day. Her weight on discharge was 6 pounds 8 ounces.

The baby was returned to the outpatient clinic several times since dismissal from the hospital, and on the last outpatient visit she weighed 7 pounds 12 ounces—at the age of 3 months 1 week. The baby is now eating cereals, meats, and is having no difficulties.

TREATMENT

The treatment of tracheo-esophageal fistula has known numerous advancements. In lieu of the poor results from surgery in 1792 when the first case of this type was reported by Richter,[25] medical treatment was all that was available and consisted of attempts to keep the child from choking to death and an attempt to maintain nutrition—both being unsuccessful. The next advancement came with surgery and anesthesia, lowering the mortality rate. This step was gastrostomy, as performed by Brennemann in 1913. Many other types of surgery were tried. No survivors were reported until 1939 when Imperatori[12] reported a case of an 8-year-old child with fistula in the lower cervical region. The approach was through the neck. Two separate attempts were necessary, but permanent restoration was finally effected and the child returned to good health.

Clerf[4] in 1933 closed the tracheo-esophageal fistula by cauterizing the opening on the esophageal side with silver nitrate.

Haight[8] in 1948 apparently was the first to successfully close a thoracotracheoesophageal fistula surgically via the extrapleural approach.

In 1951 Helmsworth and Pryles[10] reported what appears to be the first successful transpleural closure of the tracheo-esophageal fistula without atresia, the patient being 6 months of age.

The present approach used is through a classical thoracotomy incision with transpleural dissection. The exposure is best, and with blood transfusion and anesthesia as safe as they are, the results of surgical treatment of tracheo-esophageal fistula without atresia are successful if the diagnosis can be made before the child is moribund from pneumonia and other complications. The actual procedure consists mainly of leaving a cuff on the tracheal side, thus facilitating easier closure, there being only one layer of sutures possible. Antibiotics make this ap-

proach possible without apprehension about postoperative infection. Intercostal drainage is mandatory. The most recent single development which has helped save these patients is the insertion of a polyethelene feeding tube down the esophagus and through the pylorus, if possible, thereby allowing the patient to be fed and to maintain nutrition.

POSTOPERATIVE CARE

Postoperative care in these cases consists of the usual antibiotics, and blood if necessary; otherwise, no fluids parenterally. Formula can be given by feeding tube on the first or second postoperative day and the feeding tube can be removed on the tenth to the twelfth postoperative day when the baby may eat normally. The usual postoperative care for thoracotomy patients must be observed.

TABLE I

DATE	AUTHOR	CASES REPORTED
1792	Cautley	6
	Pass	1
1933	McKinney	1
	Imperatori	1
	Gengenbach and Dobos	2
1946	Leven and Lannin	2
	Shaw	1
1946	Holt, Haight and Hodges	1
	Barkely	1
1950	Morton, Osborne and Klassen	1
1950	Cardullo and Berens	1
1951	Helmsworth and Pryles	1
1951	Leigh, Abbott and Hopkins	2
1951	Knox	1
1952	Robb	1
1953	Colt, Hart, and Mayer	1
	Total	24

It is of interest to note that an x-ray with Lipiodol was done previous to the child's hospitalization here. This, however, failed to reveal the fistulous communication, probably because the Lipiodol was introduced via the plastic tube in the esophagus with the lower end of the tube several centimeters below the fistula.

We have found twenty-three previously reported H-type tracheo-esophageal fistulas without esophageal atresia reported in the literature. They are shown in Table I.

SUMMARY

We have presented a report of the diagnosis and surgical repair of a case of tracheo-esophageal fistula without esophageal atresia (H type, or fifth type). We have called attention to the fact that this is a rare type of anomaly and that there are twenty-three previously reported cases. It is pointed out that this is the type of tracheo-esophageal fistula that bears the best prognosis and is the most easily repaired, surgically.

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CORONARY THROMBOSIS IN A FIVE-MONTH-OLD INFANT

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THIS case of coronary thrombosis in an infant is presented as another instance of sudden death in infancy and childhood. Coronary occlusion in infants is more common than might be suspected, having been reported by several authors.[1-10] Coronary thrombosis due to inflammatory disease, and especially to rheumatic fever, is, however, relatively rare, three cases being reported by Gross and associates[9] and one by Rae.[10]

CASE REPORT

J. T., a 5-month-old male, had been delivered spontaneously at term after a normal pregnancy. This was the mother's first pregnancy. The neonatal period was uneventful. The mother noticed during the first two months after birth that the baby seemed to cry a lot while nursing and frequently choked. He was never cyanotic, however. He had had "colic" frequently with crying and cold sweats. She also noted that beginning at 2 weeks of age, the baby seemed to prefer to be held upright in her arms rather than in a reclining position.

About one month prior to his first visit to U.S. Naval Hospital, San Diego, the infant had an illness called "flu" by his parents. This lasted two weeks and was characterized by fever, vomiting, loose stools, and dry skin. He was treated by a private physician and at another military dispensary with penicillin and seemed to recover satisfactorily.

Two weeks before he was seen here, he had a two-day illness which seemed similar to his presenting complaints. He had been irritable, "groaned" a lot, refused to eat, and vomited several times. He had no fever. He recovered from this and seemed well until two days before entry here.

Two days prior to admission, he slid to the floor from a high chair, striking his head. He cried at once. He was said to be partly protected in the fall by a blanket. That morning he vomited once.

The day before admission, he vomited once in the morning, and later in the day became irritable, "groaned" again, and generally seemed ill. He coughed a little and the parents noted that he "broke out in a cold sweat." During the evening he vomited repeatedly. At 4:45A.M. he was brought to the emergency room of the outpatient department because no improvement had been noted and the parents thought he had seemed slightly cyanotic for about one hour before the examination.

The initial examination revealed an alert infant with grunting respirations and good color. Rectal temperature was 100.4° F. The fontanel was soft. Before the examination could be completed, the infant suddenly extended his arms and respiration ceased. Heart sounds stopped at almost the same time. Oxygen by mask and intracardiac epinephrine were given at once followed by artificial respiration, but there was no response and the infant died.

The family history was noncontributory with the following possible exception. Twin sisters of the mother died suddenly—one at 1 year of age, the other at 2 years. The cause was said to be "some germ in the milk." We

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The opinions herein expressed are those of the author and do not necessarily represent the views of the U. S. Navy Department or the military establishment.

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were unable to obtain further information on these children.

Report of Autopsy.—Gross description: The abdomen contained 15 c.c. clear yellow fluid. The organs were grossly normal in appearance. There was no free fluid in the thorax. The mediastinum was normal. There was 55 c.c. of clear pericardial fluid. The lungs did not appear abnormal.

The heart weighed 77 grams. The epicardial surface was slightly pale, and on the posterior aspect of the left ventricle just below the atrioventricular sulcus there was a row of petechiae. Posterior to the base of the pulmonary artery there was a swelling seen on the epicardial surface, which appeared somewhat fusiform and was elevated 0.5 cm. above the surrounding surface. It was approximately 1.0 cm. wide in the region of the atrioventricular sulcus, and tapered downward to disappear approximately 1.5 cm. below this point. The great vessels were normal in their arrangement, the ductus arteriosus was closed, and the foramen ovale was also closed. The endocardium of both ventricles was pale and thickened. The cardiac chambers were normal in their general arrangement and appeared somewhat dilated. The valves were not remarkable. An incision into the area of swelling in the region of the left coronary artery revealed this to be a greatly dilated and occluded artery (Fig. 1). The left coronary ostium was normally placed and measured 0.1 cm. in diameter. Immediately distal to the ostium the artery dilated to a diameter of about 1.0 cm. This dilatation included the area of bifurcation of the artery and continued distally as the upper portion of the anterior descending branch. The dilated anterior descending artery began to narrow after approximately 1 cm., so that at a point between 2.0 and 2.5 cm. from the ostium, it was 0.1 cm. in diameter, and appeared more nearly normal. The dilated portion was filled with dark, clotted blood which was slightly friable. The circumflex artery branched off at a normal distance from the ostium and emerged from the dilated area. It was slightly irregular on its cut surface, which measured 0.3 by 0.4 cm. Its wall was fixed and yellow, and its lumen was slightly flattened, measuring 0.1 by 0.15 cm., and was occluded by a thrombus.

The right coronary artery arose normally and its ostium was between 0.1 and 0.5 cm. in diameter. The wall of the artery was thick and yellow, and the total diameter of the vessel in its first 1 cm. of length was 0.6 cm. The lumen was eccentrically placed and measured 0.15 by 0.2 cm. on its cross section. The lumen was filled with a clot which was rather recent in origin.

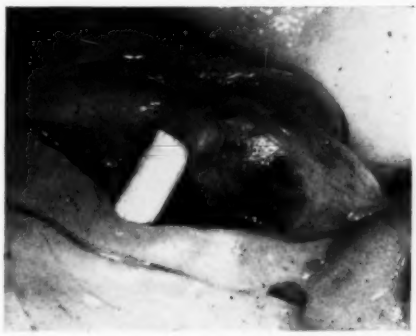

Fig. 1.—Section through the dilated, thick walled left coronary artery with thrombosis.

The myocardium was slightly pale, the left ventricle measuring up to 0.8 cm. in thickness and the right ventricle averaging 0.2 cm. There were rather widespread areas of hemorrhage in the myocardium which were seen on the cut surfaces, but for the most part did not appear on the epicardial or endocardial surfaces. These areas of hemorrhage were seen in both the anterior and posterior portions of the interventricular septum and in the greater portion of the posterior wall of the left ventricle.

Post-mortem blood culture revealed no growth.

Summary of microscopic findings: Sections of the heart revealed a widespread degeneration of muscle fibers, amounting in some areas to a massive necrosis. In addition, a marked inflammatory process was seen. This inflammation did not have the appearance of that which would be expected merely in response to a myocardial infarction. Large numbers of large mononuclear cells were seen, as well as considerable numbers of lymphocytes. Very few areas were found which contained significant numbers of segmented neutrophils.

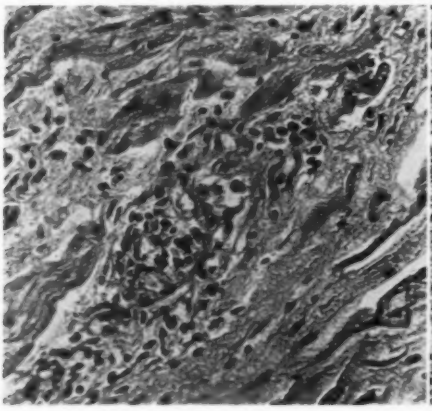

Fig. 2.

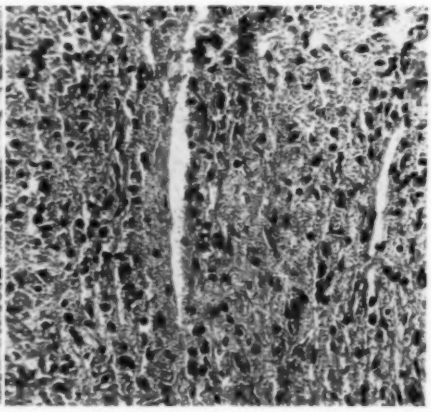

Fig. 3.

Figs. 2 and 3.—Photomicrographs of sections of the myocardium showing degenerative muscle fibers and lymphocytic and mononuclear infiltration. (×450; reduced ⅙.)

No distinct Aschoff bodies were seen, but the grouping of some of the mononuclear cells was suggestive, as well as their individual appearance (Figs. 2 and 3). In addition to the severe myocarditis, a marked endocarditis was present, including involvement of the endocardium of the left auricle. Many of the small intramuscular branches of the coronary arteries showed inflammatory and degenerative changes, but thrombosis of these branches did not appear to have taken place. Sections of the left coronary artery taken proximal and distal to its first bifurcation showed an almost complete loss of the muscularis with replacement by inflammatory tissue. Aneurysmal dilatation appeared to have taken place, with a partial occlusion of the lumen by a thrombus which was in the early stages of organization, and with completion of the occlusion by a more recent thrombus. Sections from the thoracic aorta revealed an inflammatory infiltration involving chiefly the intimal layer, with slight but definite thickening of that layer. A few inflammatory cells were also seen scattered throughout the muscularis.

Sections of the lungs revealed a patchy atelectasis of moderate degree, and an inflammatory exudate consisting of edema fluid and mononuclear cells. There were a few isolated foci of acute inflammation, with large numbers of polymorphonuclears, but elsewhere these cells were virtually absent. This pneumonitis had no distinctive features in that it was not diagnostic of any one condition. A few alveoli showed a suggestion of a hyaline membrane formation, but this was not a marked feature at all.

Sections of the other organs revealed no noteworthy changes. Specificially,

the arteritis which was so striking in the heart was not reflected in the other organs at all.

Although the gross impression was that we were dealing with an arteriosclerotic process, with occlusion of the coronaries on that basis, the microscopic picture was instead one of a predominantly inflammatory process. Besides manifesting itself in the form of a severe myocarditis and endocarditis, this inflammatory process also took the form of a severe arteritis, involving chiefly the coronaries but also the aorta. Aneurysmal dilatation of the proximal portions of both major coronary vessels ensued, followed by their complete occlusion. A certain portion of the myocardial destruction may well have been due to this interference with circulation, but it was certain that a great portion of it was inflammatory in nature and antedated the terminal coronary occlusion.

DISCUSSION

Stryker[8] gave an excellent review and summary of the problem of coronary occlusion in childhood in 1946. He listed the following lesions which may cause partial or complete occlusion:

1. Medial calcification with fibroblastic proliferation of the intima.
2. Polyarteritis (or periarteritis) nodosa.
3. Arteriosclerosis (atherosclerosis).
4. Syphilitic arteritis.
5. Embolism.
6. Congenital abnormalities.
7. Rheumatic arteritis.
8. Hypertension.

The third cause listed above is the most common cause in adults, but is relatively rare in infants and children. Stryker stated that "the only cause of coronary occlusive disease in adults not described in any person below age 17 is thromboangiitis obliterans (Buerger's disease)."

Most of the cases of coronary occlusive disease in infants reported appear to be due to medial calcification with fibroblastic proliferation of the intima. Gross and associates,[9] in a report on the pathologic changes occurring in the coronary arteries in rheumatic fever, mention two cases of thrombosis with myocardial infarction occurring in children aged 17½ months and 7½ years. Rae[10] reported a child of 33 months who had previously had occasional "blue spells" and whose terminal illness was characterized by fever, joint pains, diarrhea, cough, and a very high white blood count. Death occurred suddenly. Autopsy revealed aneurysms of the right and left coronary arteries with a thrombus in the right. There were inflammatory lesions of proliferative, degenerative, and necrotic character. There was generalized evidence of rheumatic fever with typical Aschoff bodies, myocarditis, and pericarditis, in addition to the arteritis.

Our case appears to compare closely in clinical course and pathologic findings with those cases ascribed to rheumatic fever by Gross and co-workers and Rae. There were no definite Aschoff bodies found and the changes of arteritis were limited rather sharply to the heart and thoracic aorta. While we cannot be certain, we feel that the changes found could be due to rheumatic fever.

Clinically it is interesting to speculate whether the child's desire to be held upright rather than in a reclining position during the first few weeks may actually have been orthopnea and was one of his earliest symptoms. The subsequent illness called "flu" very likely was actually an active phase of

the myocarditis and endocarditis and the older thrombus seen at autopsy may well have occurred at that time.

SUMMARY

A case of coronary thrombosis resulting from an acute myocarditis, endocarditis, and coronary arteritis possibly due to rheumatic fever in a 5-month-old infant has been presented. A review of the literature shows that coronary occlusive disease in the very young is somewhat more common than one might suspect from the usual brief mention it receives in most pediatric texts. Rheumatic fever as a cause of coronary occlusive disease in infants is comparatively rare, there being only three cases reported previously.

I am indebted to Commander W. F. Pierce (MC), USN, and Commander C. S. Hascall, Jr. (MC), USN, of the Department of Pathology of the U.S. Naval Hospital, San Diego, for the complete pathologic study and report of this case.

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UVEITIS ASSOCIATED WITH CHICKEN POX

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UVEITIS in children is uncommon. Of 810 cases surveyed by Kimura and associates,[1] only forty-seven, or 5.8 per cent, were in patients under 16 years of age. The authors realize that this is much higher than the general average of other studies which are quoted as being approximately 2 to 3 per cent.

About one-third of the completely studied cases have a presumptive or definite diagnosis, while the remaining two-thirds are unexplained. For the most part, the scanty literature on this subject makes mention of uveitis in association with toxoplasmosis, Boeck's sarcoidosis, juvenile rheumatoid arthritis (Still's disease), syphilis, and brucellosis.

Ravin[2] describes a case of uveitis which developed during measles. Roussel[3] reports one case of uveitis in a patient convalescing from mumps. Hallett[4] reports a case of unilateral uveitis during chicken pox. Duke-Elder[5] refers to a case by Hutchinson in his textbook of a twenty-one-month-old child with chicken pox who developed bilateral uveitis.

CASE REPORT

C. P. (No. 192-266), a 6-year-old boy, was first seen on May 30, 1954, because of a generalized papulovesicular rash. This was apparently the first day of illness, and a diagnosis of uncomplicated chicken pox was obvious. The following day, an inflammation of the left eye was noticed by the mother, but since the child experienced no discomfort, a medical opinion was not sought at this time. A week later, however, the left pupil became fixed and dilated. The inflammation persisted, so the boy was brought back to our clinic and a diagnosis of unilateral uveitis was made. The chicken pox was now in the convalescent stage with only a few crusted lesions still present.

An examination by our consultant ophthalmologist, Dr. R. Stump, revealed 20/25 visual acuity on the right and 20/50 on the left. The right globe was completely normal. The left bulbar conjunctiva showed a moderately severe flush which fanned out from the periphery of the iris onto the sclera. Upon biomicroscopic examination of this eye, a hazy aqueous and vitreous with dustlike uveal precipitates were seen. The pupil measured 5 mm. in diameter and was fixed. Tension to finger palpation was normal. Funduscopy revealed edema of the retina in the central regions. There was no secretion from the eye, and the closest manifestation of varicella was on the middle of the forehead and the right eyebrow.

The child was admitted to the hospital on June 8. Cortisone was started intramuscularly and in a 2½ per cent eyedrop solution. Large doses of aspirin, 1 per cent atropine sulfate eyedrops, and daily penicillin were also prescribed. By the next day a marked clearing in the inflammatory process was already noticed but the pupil remained dilated and fixed. Inadvertently, the atropine drops were not started until after this examination so that the dilatation of the pupil was a real one (Fig. 1).

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Four days after admission, the globe was perfectly white and the aqueous and vitreous clear. The retinal edema had subsided in part. As this improvement continued, the patient was weaned from the parenteral cortisone and discharged June 18 on the atropine and cortisone eyedrops. By June 28, almost one month from its onset, the process was considered to be completely quiescent with no apparent residua. The vision was now 20/25 in both eyes.

The following laboratory examinations were done: chest x-ray, normal; x-ray of the left orbit, negative for foreign body; complete blood counts, normal; bleeding and coagulation times, normal; total eosinophil counts followed throughout the course of cortisone therapy were within normal limits with a normal adrenal response; urinalyses, normal; tuberculin skin tests, negative in all strengths; blood serology and agglutinations were all negative.

Physical examinations were consistently negative for other foci of infection. The paranasal sinuses transilluminated normally, and the teeth were in good repair. His background was negative for allergy or any other significant illnesses.

Fig. 1.—Unilateral iritis, left. The pupil is dilated, fixed, and irregular.

COMMENT

Although the specific cause and effect between uveitis and chicken pox cannot be proved, it seems very probable that the two were related in this patient. No other cause was found to explain this complication. Local involvement of the eyes by the varicelliform lesions did not occur, so one must assume that the inflammatory process was on the basis of a generalized viremia.

SUMMARY

This is the third case of uveitis to be added to the literature which occurred as a complication of chicken pox, and the fifth to be associated with any of the childhood contagious diseases.

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NEURORETINITIS FOLLOWING MEASLES

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OPTIC neuritis and neuroretinitis occurring shortly after an attack of measles are generally considered to be manifestations of measles encephalitis. These unusual complications are not even mentioned in most descriptions of the disease. Neuroretinitis is much more unusual than optic neuritis. Only nine possible cases of neuroretinitis have been reported.[1-8] None have been reported in an English language pediatric journal. To my knowledge, there is one instance of neuroretinitis which has not been reported.[9] Most reported instances of blindness associated with measles have been considered incidental to a predominantly encephalitic picture. Neuroretinitis following measles, with little or no evidence of encephalitis, thus appears to be a very unusual occurrence.

CASE REPORT

P. C., a 6-year-old white girl, had had a moderately severe attack of measles seven days prior to her admission to the contagious disease section* of Delaware County Hospital on June 14, 1954. The acute episode of measles was typical. Fever, cough, coryza, conjunctivitis, and Koplik spots preceded the usual morbilliform rash. The incidence of measles was higher than usual in the child's school at this time. One day prior to admission, she complained of a mild headache, pain on moving her eyes, and loss of vision. The parents noticed redness of the eyeballs and enlarged pupils. There were no other complaints.

On admission to the hospital, the patient's pulse was 95, respirations 20, and the temperature 98.8° F. Examination of the heart, lungs, and abdomen revealed no pathologic findings. All the cranial nerves except the optic nerve were intact. There was no nuchal rigidity or Kernig's sign. Sensory and motor functions were all normal, as were the tendon reflexes.

The external ocular examination was as follows: The vision was limited to light perception in both eyes. There was faulty projection of the light. The conjunctival and scleral vessels were engorged; the pupils were 8 mm., equal, and barely reacted to light. Normal lid and corneal reflexes were present. There were no extraocular muscle palsies or any nystagmus.

The fundi showed slight hyperemia of the optic nerve heads. The discs were well outlined and venous pulsations were present. The vessels were full and somewhat tortuous. The veins were more dilated than the arteries. No hemorrhages were seen, but diffuse retinal edema was present.

The blood count and urinalysis were within normal limits.

A tentative diagnosis of retrobulbar neuritis was considered.

The patient was placed on ACTH gel 50 mg. b.i.d., given a daily dose of 2 c.c. of gamma globulin for three days, and general supportive treatment. During the first two days of hospitalization the patient slept fre-

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*Service of Edwin W. Rodenheiser, M.D., Director of Communicable Diseases, Delaware County Hospital.

quently, but could be easily aroused. By the fourth day the dilated vessels of the selera, the hyperemia of the disc, and the engorgement of the retinal vessels had disappeared. The pupils reacted more readily, but the patient's vision was still limited to light perception. At times, however, she stated that she could not see the light.

The retinal edema persisted. A small, shiny exudate about the size of a retinal vessel appeared in the right macula. A similar exudate along with a slightly larger one appeared in the left macular region. It became apparent that this patient probably had a neuroretinitis, rather than an optic neuritis. Subsequent events confirmed this impression.

very gratifying. The patient was allowed out of bed, she watched television, and could identify large colored objects. The estimated vision was about 6/60. The pupillary reactions were normal in strength, but slightly delayed.

The patient was discharged at the end of the third week. During her hospital stay her temperature varied from 98.6° to 99.8° F. The white cells of the blood ranged from 6,800 to 16,400 per cubic millimeter; the differential count was normal. No abnormal neurological findings were present at any time.

After the child was discharged from the hospital, she complained of night blindness. During the day she would also bump into furniture if she

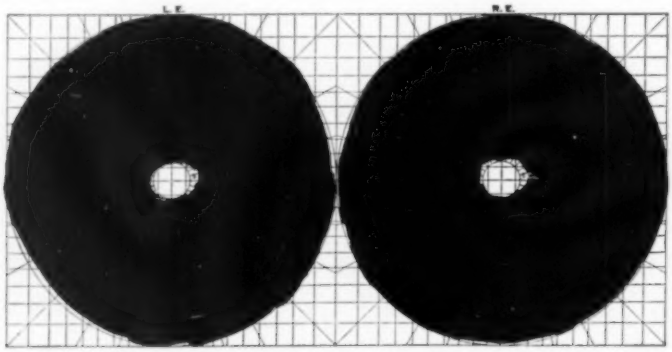

Fig. 1.—Visual fields of P. C. showing remaining central area of vision of about 8. Vision 6/9 in each eye. Ten millimeter white test object used at one meter.

During the second week, 250 c.c. of plasma and three doses of 2 c.c. of Protamide were given in addition to the ACTH gel. Light perception by the end of the second week was better, and at times the patient said she could see certain distant objects. At close range she could see practically nothing.

At the beginning of the third week trypsin was given intramuscularly. The dose of ACTH gel was gradually reduced and the administration of oral cortisone started. The improvement in vision during this week was

did not move slowly or look directly at the object.

The central vision continued to improve and within six weeks, her vision was 6/9 in each eye and she could distinguish the colors of 1 mm. test objects.

Central vision fields were taken and showed that the child only had vision within 8 degrees of fixation. The peripheral fields were completely obliterated as shown in Fig. 1. Funduscopic examination now revealed the reason for the markedly constricted fields. The discs were normal in color

and outline. The retinal arteries were somewhat attenuated. Both fovea had a slightly granular appearance. The remainder of each retina had a diffuse fine pigmentation, appearing as though someone had scattered pepper over it. This unusual pigmentation was first suspected shortly after the patient was discharged from the hospital. It became more marked during the following month and has persisted to the present.

COMMENT

Ström[1] and Stewens[2] have each reported a case of neuroretinitis following measles. These two patients had a "star-shaped" figure in the macula during the course of the disease. This "star" figure is similar to that seen in renal retinopathy. The vision only returned to about 6/60 in each of these cases. Scheie[9] has also recently seen a case of "stellate" retinopathy following measles. Retinal edema was prominent in the cases reported by Sottow,[3] Horner,[6] Heath,[4] and Shlossberg, and Prizer,[5] but no stellate figure in the macula was present.

The patient seen by Sottow was first examined two and one-half months after an attack of measles. At this time there was marked pigmentation of the peripheral retina similar to that seen in retinitis pigmentosa. The peripheral fields were markedly constricted. Bischler[7] and Thums[8] have reported three patients with retinitis pigmentosa following measles. The latter author's two cases were not seen during the acute phases. One of them might have been the result of hereditary factors rather than a complication of measles.

Those patients seen during the acute phases of the disease had a very rapid and profound loss of vision. Even light perception was questionable in some.

Other neurological evidences of encephalitis were present in only two[3, 4] of the other ten patients. Return of vision begins about two weeks after the onset and may be quite rapid. The extent of recovery, however, is quite variable and the prognosis should be guarded.

Fortunately, this serious complication of measles is rare. Its occurrence is a further reminder that measles is not always an innocuous disease.

I wish to thank Dr. Caroline Vetkoskey for the opportunity of following this child's eye condition.

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CERVICAL HERNIA OF THE LUNGS

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THERE has been recently a renewed interest concerning hernias of the lungs. Most of the reported cases, however, were of the acquired type and the majority of them concerned adults.[1, 2, 3] The case reported by Palazzo and Garrett[4] concerned an infant with multiple congenital anomalies, where the pulmonary herniation could be "explained" as one of the many manifestations of deviation from the normal. Baldi and Gadea[5] described a case of pulmonary hernia due to partial agenesia of the ribs.

As our present case is that of an otherwise perfectly normal girl whose progress has been followed at the clinic for more than three years, we thought it might be worth reporting.

Hernia of the lungs may be defined as "a protrusion of the pleura-covered lung beyond its normal boundaries through an abnormal opening in the thoracic enclosure."[3] More than 100 years ago, Morel-Lavalée classified pulmonary hernias as follows:

I. According to Location
   A. Cervical (commonly congenital)
   B. Thoracic (mostly traumatic)
   C. Diaphragmatic (extremely rare)
II. According to Etiology
   A. Congenital
   B. Acquired
      1. Traumatic
      2. Consecutive (following healing of a wound)
      3. Spontaneous (congenital weakness, plus increasing pressure)
      4. Pathologic (result of inflammatory process or malignancy)

A detailed description of the various categories, as well as an analysis of eleven cases, can be found in the article by Maurer and Blades.[1] Lozar[7] suggests that mediastinal hernia should be included in the acquired group. This is the type of hernia frequently seen in pneumothorax therapy of pulmonary tuberculosis. In their extensive review of the older literature, Montgomery and Lutz[8] found approximately one-third of the cases in individuals under 15 years of age. The male:female ratio in the entire group was 3:1 due probably to the greater traumatic exposure of the males.

The mode of occurrence in their 165 cases was distributed as follows: 29 congenital or early acquired, 83 traumatic, and 53 spontaneous, single unilateral or bilateral.

In seventy-nine cases, of which the location was definitely mentioned, the relative incidence was: 16 cervical (10 right, 6 left), 62 thoracic, and 1 diaphragmatic. Cervical hernias represent the majority of the congenital or early acquired group. They

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can be detected in the neonatal period, but as the lungs are in a state of collapse during intrauterine life, there is often no evidence of a hernia until some time after birth.

In later childhood or adult life two factors are operating for the production of spontaneous pneumocele:

(1) Lowered resistance of the thoracic wall, due to developmental factors.

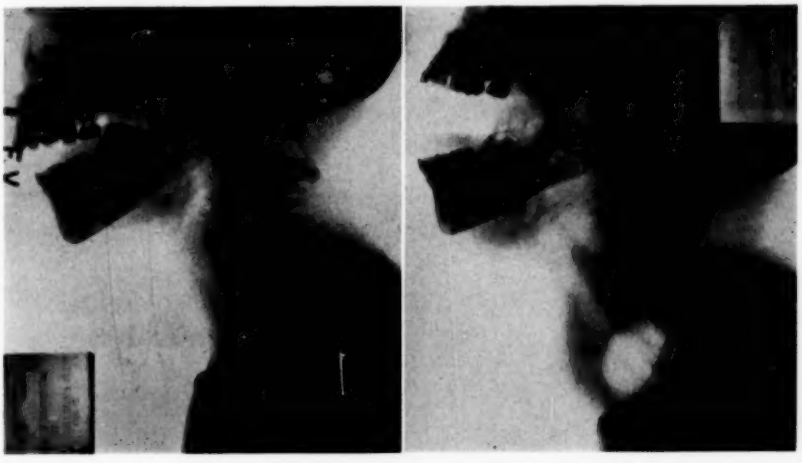
(2) Abnormal or prolonged increase in intrathoracic pressure.

Most common areas of anatomic weakness are the superior aperture of the thoracic cage and the intercostal spaces in the anterior chest wall, medial to the costochondral junction. In hernias occurring through the superior aperture of the thorax, the lung finds its way in the interval between the sternocleidomastoid and scalenus anticus muscles, following some tear or deficiency in Sibson's fascia, which normally limits the cervical excursion of the pleura and lung.[1, 3, 9]

We believe our case to be one of spontaneous development of a bilateral hernia, resulting from a congenital weakness of Sibson's fascia, plus a chronic intermittent spasmodic increase in intrathoracic pressure due to recurrent spells of coughing.

CASE REPORT

M. A. V. was first seen in the Children's Clinic on Sept. 24, 1951, at the age of 4½ years. For the past two years her mother had noted a "lump" in the girl's throat whenever she coughed, laughed, or talked loud. For the two weeks preceding her visit, the lump seemed to have become larger and more prominent. She was born Jan. 17, 1947, after an uneventful pregnancy and a normal delivery. Birth weight was 9 pounds. No abnormalities were noted at birth. Nutrition, growth, and development were reported as normal. She had no respiratory infections during the first



A. *B.*

Fig. 1.—Lateral roentgenograms of the cervical area taken Sept. 24, 1951. In *A* no abnormality is seen. In *B*, taken during coughing, the pulmonary tissue is seen bulging over the clavical, up to the superior margin of T-1.

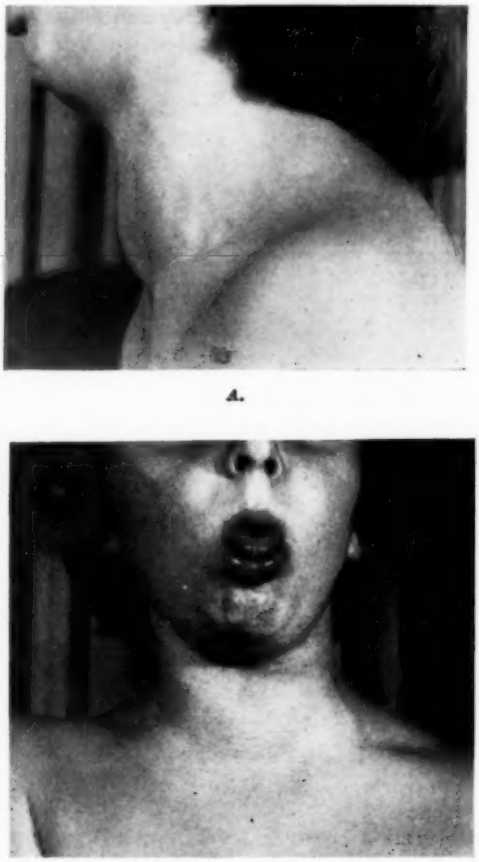
year of life. She had never complained of difficulty in swallowing and the bowels had always moved regularly. Of the contagious diseases she had contracted only chicken pox.

For several years (number not specified) she had been suffering from a seasonal cough. Her mother had been told it was an "allergic bronchitis."

Family history revealed allergy on the paternal side.

Physical examination revealed a 4½-year-old white girl, weight 23.6 kilograms and height 115 centimeters. Temperature was normal. Ear, nose, and throat: slightly hyperemic nasopharyngeal mucosa. Lungs were clear; heart, no abnormal findings. Blood pressure, right arm was 95/70, left arm 95/60.

When the patient coughed, a large lemon-sized mass protruded above the sternum in the midline. It was



A.

B.

Fig. 2.—Photographs of M. A. V. taken March, 1954. In the lateral view (*A*) the hernia is shown protruding over the sternal notch during coughing. The same, although less clearly, can be seen in *B*.

soft, spongy, compressible, and somewhat crepitant. It did not fluctuate and there was no tenderness. The skin covering it was normal. The thyroid gland was not palpable. Urinalysis and blood counts were normal. Sedimentation rate was 12 mm. Serologic tests for syphilis were negative.

X-ray examination: Lateral views were taken of the neck in the neutral position and during coughing. The conventional film revealed no abnormality. The films taken during coughing, however, revealed considerable soft tissue prominence, anteriorly, just above the clavicles, with ballooning of the lung tissues to the level of the superior margin of T-1. The outline of the trachea was readily identified through the distended lung tissues. Its contour was not remarkable. Anteroposterior films taken during coughing were not satisfactory, in spite of repeated attempts.

The conventional six-foot chest film taken during full inspiration revealed no abnormality.

Fluoroscopic examination of the chest and cervical area confirmed the findings previously reported. In the anteroposterior view, under the fluoroscope it was determined that both lungs were involved in the herniation process in almost equal degree.

Following the first visits, the patient continued to be seen at the clinic in regular intervals for observation. When indicated, pyribenzamine expectorant, Cheracol, and elixir terpin hydrate with codeine were prescribed to control coughing, with satisfactory results. Subsequently, she seldom complained of severe cough, and expectoration was scarce. In June, 1953, she had her tonsils and adenoids removed. Her life was that of the average healthy girl, except for the fact that she had been instructed to avoid strain of any kind. On her last visit, June, 1954, she showed very satisfactory growth (weight 31.5 kilograms and height 133 centimeters), and system review revealed no pathologic findings.

Repeated roentgenologic examination of the chest and cervical region revealed noticeable improvement in the degree of herniation of the lungs. Although the amount of intrathoracic pressure she exercised for the occasion was essentially the same as in previous examinations, there was no significant bulge of the soft tissues and the amount of lung tissue in the

A. *B.*

Fig. 3.—*A*, Conventional film of the chest revealed no abnormalities. *B*, Film taken on June 16, 1954, during straining shows decrease in the size of the hernia.

base of the neck was definitely less than in the initial examination in June, 1951. The bony framework, trachea, great vessels, heart, and diaphragm were not remarkable. The lung fields were clear.

SUMMARY AND CONCLUSION

The case of a bilateral cervical hernia of the lungs is presented. Herniation was first noted by the mother at 2½ years of age. It progressively increased in size, a chronic cough being probably a contributing factor. After coughing was successfully controlled and straining, in general, avoided, the degree of herniation remained stationary and gradually it seems to have decreased in size. It is believed that there might have been some degree of spontaneous reinforcement of the defective fascia.

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Accidental Burns

January 1, 1739. One Day last Week a Woman at the North End, having sat her young Child before the Fire and left it alone, while she stept out about some Business, in which Time a Spark of Fire flew upon the Child's Cloaths, and before it's Mother return'd, it had spread and got thro' to the Flesh, so that the poor Child's Legs were burnt in a most terrible manner, and 'tis tho't they must both be cut off in order to save it's Life.

January 8, 1739. The Child whose Legs were so terribly burnt, as mentioned in our last, as 'twas Tho't they must have been cut off to save it's Life, dyed last Monday Morning; part of one Foot having been cut off the Day before, and the whole of the other was to have been cut off to the Ankle the next Day, if the Child had liv'd.

BOSTON WEEKLY POST BOY.

December 2, 1747. My son Ebenezer fell into the Fire his Hands were both burnt—great pain & Smarting. For his relief I immediately kill'd a Cat & he washed his Hands in the Blood.

EBENEZER PARKMAN'S DIARY.

Medical Progress

A REVIEW OF BCG AND OTHER ANTITUBERCULOSIS VACCINES

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NUMEROUS agents have been acclaimed as showing promise of fulfilling the many criteria needed to be met by a vaccine against tuberculosis. However, the majority of these have failed to survive as dependable and practical agents. After the isolation of the tubercle bacillus by Robert Koch[1] in 1882, it was hoped that means of prevention and cure of tuberculosis would soon be forthcoming. Attempts to use a bacillary extract (Koch's old tuberculin) were a logical consequence, but the trials with tuberculin for both prophylactic[2] and therapeutic[3] purposes soon ended in failure.

The more important attempts to produce vaccines against tuberculosis can best be classified according to the type of antigen used. Most investigators have employed suspensions of either nonviable or living tubercle bacilli as an antigen. It is true, however, that especially in the older literature one finds many references to the use of "modified" bacilli; often there was no clear indication as to whether or not the bacilli were viable when used. As early as 1886, Cavagnis[4] attempted to immunize guinea pigs and rabbits with a vaccine which he had produced by treating tubercle bacilli in sputum with varying strengths of carbolic acid. Absolute immunity, which was the goal sought, could not be demonstrated. In 1924, Calmette and associates[5] listed some of the agents that had been tried in an effort to modify tubercle bacilli so that they would be incapable of producing progressive tuberculosis when administered to animals, yet would confer resistance to the disease. The agents used to modify the organisms included iodine, sodium fluoride, glycerin, galactose, soaps, chlorine, and light radiations; none of these were effective.

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VACCINES CONTAINING NONVIABLE TUBERCLE BACILLI

Of the vaccines employing nonviable tubercle bacilli as an antigen, those based on the injection of heat-killed organisms have undoubtedly been utilized most often. Zinsser and co-workers,[6] Petroff and associates,[7] and others during the 1920's claimed to have obtained experimental evidence in animals indicating that heat-killed tubercle bacilli produced some resistance to tuberculous infection. However, Calmette,[8] Smith,[9] and most workers in the field supported the contention that any protection conferred by heat-killed tubercle bacilli was neither sufficiently strong nor prolonged to be of practical value. Views as to the capacity of heat-killed organisms to produce

either hypersensitivity or immunity at that time were, at best, conflicting.[10] In recent years, Wells and associates[11] have reported on the injection of patients in Jamaica with heat-killed tubercle bacilli. Though various authors believed their results were encouraging, almost all workers have failed to accept vaccines consisting of heat-killed tubercle bacilli as being dependable.

As early as 1906, Di Donna[12] attempted to immunize guinea pigs with tubercle bacilli rendered nonviable by prolonged exposure to sunlight. Di Donna, as well as Smithburn and Lavin,[13] who in 1939 reported experiments utilizing tubercle bacilli as antigens which had been rendered nonviable by exposure to ultraviolet light, failed to demonstrate resistance to tuberculosis in experimental animals with these nonviable irradiated bacilli. In 1947, Olson and collaborators[14] of the United States Public Health Service and, more recently, Sarber and associates[15] and Milzer and associates[16] have reported the use in experimental animals of vaccines containing nonviable human tubercle bacilli which had been killed with extremely short exposure to ultraviolet light. These workers noted resistance in the vaccinated animals to a subsequent virulent infection with tubercle bacilli when the vaccinated groups were compared with nonvaccinated control animals. These reports have raised hopes once again that a successful nonviable antituberculosis vaccine might have been found, but thus far subsequent encouraging reports with these irradiated nonviable vaccines have not been forthcoming.[17, 18] No vaccine containing nonviable tubercle bacilli as an antigen has ever been proved to consistently produce acquired resistance to tuberculosis in man.

VACCINES CONTAINING VIABLE TUBERCLE BACILLI

In 1907, Albert Calmette and Camille Guérin[19] at the Pasteur Institute in Paris reported that, in their opinion, a primary infection with tuberculosis produced resistance in the body of the host against reinfection. The writers felt that they could produce limited immunity in cattle by inoculating the animals with virulent tubercle bacilli through an esophageal sound. Later Calmette[8] outlined the numerous attempts that had been made to confer resistance on animals or man with viable virulent organisms prior to 1923. These included graduated doses of living tubercle bacilli of the human,[19] bovine,[20] and avain[21] types; however, most of the enthusiastic claims for these and similar experiments have never been consistently substantiated. It also soon became apparent that the vaccination of cattle and goats with either virulent human or bovine bacilli could lead to the dissemination of these organisms through the milk and excreta of the animals, thereby leading to possible infection in human beings.

Wells and Oxon[22] of Oxford, in 1937, reported the discovery of an acid-fast bacillus, *Mycobacterium muris*, isolated from wild voles indiginous in certain areas of Scotland. In 1946, Wells[23] summarized the immunologic studies on animals which had been conducted with *Myco. muris* (vole bacillus) as an antigen; he reported that some resist-

ance to subsequent virulent infection with a human strain of tubercle bacilli was conferred by the viable vole bacillus. Wells[24] in 1949 reported a controlled study of children and young adults who were vaccinated with the vole bacillus. He found a statistically significant resistance to subsequent tuberculous infection in this vaccinated group when compared with a nonvaccinated, tuberculin-negative control group. However, it should be noted that Young and Paterson[25] in 1947 reported progressive disease in calves, rabbits, and guinea pigs following inoculation with strain G564 of the vole bacillus. There is relatively little evidence at the present time on which to appraise adequately the value of the vole bacillus in the prevention of tuberculosis in man, although laboratory experiments with animals would appear to be encouraging. In the past it has been found that other acid-fast organisms, such as the bacillus isolated from a water turtle by Friedmann[26] and the acid-fast bacilli isolated from snakes[27] and fish,[28] have never been proved to impart satisfactory immunity to heterologous hosts.

As early as 1889, Dixon[29] stated that tubercle bacilli which had become attenuated by variations in the environment in which cultures were grown might be utilized to establish immunity in animals. During 1908, Calmette and Guérin, in Paris, started the attenuation of a virulent bovine strain of tubercle bacilli. This culture was subcultured every two weeks on glycerin-bile-potato medium. By 1922, they believed that the culture, which had been named BCG (Bacillus Calmette-Guérin), was no longer pathogenic for animals, and an experiment was undertaken in which 217 newborn infants were given BCG by mouth. This was administered in doses of 2.0 or 10.0 mg. per day for three days during the first week of life; however, no conclusions were drawn from this work except that BCG was harmless when given to infants.[5] Calves which were given BCG also were reported by Calmette and others to have resisted infection with virulent tubercle bacilli which killed control animals in six to eight weeks. These reports were soon followed by the enthusiastic and somewhat promiscuous use of BCG for the vaccination of tuberculin-negative infants and children in Europe, particularly in France and Germany. The premise on which this was done was Calmette's belief that an initial infection with tuberculosis imparted resistance to a subsequent reinfection with the disease. It was believed that if a mild nonprogressive tuberculous infection could be given to tuberculin-negative patients who had had no previous contact with tubercle bacilli, the patient would develop an acquired resistance to tuberculosis before he subsequently came in contact with virulent tubercle bacilli. Today, this premise is questioned by many physicians, but, unfortunately, this is not the only questionable point involved in BCG vaccination against tuberculosis. Calmette and Guérin, and those men who have followed them, have utilized the tuberculin test as their means of determining whether or not BCG vaccination has produced acquired resistance in the patient. This relatively nonspecific test was used because no other test was avail-

able, and it was assumed that the conversion of a patient's tuberculin reaction from negative to positive following vaccination was evidence that resistance had been acquired to tuberculosis. Unfortunately, this situation still exists today, since no practical and highly reliable test has yet been developed which can be widely used for determining an individual's acquired resistance to this disease.

The question of whether or not tuberculin hypersensitivity, as demonstrated by a positive tuberculin reaction, indicates acquired resistance to tuberculosis has remained a controversial subject despite great interest and numerous studies concerning the problem. Freund and Opie[30] state that sensitization is accelerated in rabbits by the injection of increasing quantities of heat-killed tubercle bacilli or by the same quantity of bacilli divided into several simultaneous injections. They further state that animals that are sensitized to tuberculin are usually more resistant to subsequent infection with tubercle bacilli than are normal animals, but that there is no correlation between the intensity of sensitization and the resistance of the animals. Rich[31] has reported evidence indicating that hypersensitivity and immunity are not dependent upon one another. Lurie[32] and Dubos[33] have stated that hypersensitivity is not an indispensable factor in immunity to tuberculosis but that the essential mechanism of immunity is the increased ability of the mononuclear phagocytes of the immune animals to destroy tubercle bacilli.

Helmholz[34] claimed in 1909 to have passively transferred hypersensitivity to tuberculin-negative guinea pigs by injecting blood from tuberculin-positive guinea pigs into normal guinea pigs. In 1945, Chase[35] reported that tuberculin hypersensitivity could be transferred from allergic or hypersensitive animals to normal animals through the medium of the cells obtained from a peritoneal exudate induced in the allergic animals. Lurie states that this work suggests that tuberculin hypersensitivity may be due to the excretion of small amounts of antibody from the tuberculous lesions into the circulation, where it becomes attached to the blood cells. The question of whether or not the acute inflammatory reaction which occurs at the site of infection in hypersensitive animals aids in the localization of the tuberculous infection is still unsettled. At the present time, it must be said that the relation of tuberculin allergy to immunity is still one of the most obscure aspects of the pathogenesis of tuberculosis.

In 1927, Petroff and co-workers[36] in the United States reported that they had grown a variant from a culture of BCG received directly from the Pasteur Institute in Paris. This variant was reported to produce progressive tuberculosis in guinea pigs. When their findings were supported by other investigators in the field, a major controversy ensued. Calmette maintained that BCG was a "virus fixe," as he had previously stated, and was, therefore, incapable of producing progressive tuberculosis in its attenuated form. He further charged that Petroff's results were erroneous. This development, however, with the Lubeck disaster in 1930, temporarily put an end to fur-

ther clinical trials with BCG. In Lubeck, Germany,[37] in 1930, 271 children were vaccinated by the oral route with what was presumed to be BCG. Of these 271 children, seventy-seven subsequently died of tuberculosis. A searching investigation of this catastrophy was undertaken during which it was proved beyond all doubt that the children had been vaccinated with a virulent culture of tuberculosis rather than the intended BCG, due to mixing of the cultures in a laboratory. Although BCG was completely freed of any blame in the Lubeck disaster, sufficient doubts were raised that the vaccine was little used in the next few years.

The primary stimulus for the renewed interest in BCG vaccination following the Lubeck disaster stemmed from the Scandinavian countries, the work of Heimbeck, Holm, and later, Wallgren, being outstanding. During the past twenty years, there have been many studies conducted on both experimental animals and human beings involving vaccination with BCG. There have been numerous reports of the production of resistance against experimental tuberculosis in experimental animals by vaccination with BCG. These reports have so consistently indicated a relative resistance to a subsequent virulent infection when compared with nonvaccinated control animals that such results are almost incontestable. Those of Birkhaug,[38] Schwabacher and Wilson,[39] Jensen,[40] Negre and Bretey,[41] Feldman and Karlson,[42] and Seagle and associates[18] can be cited as well as others. It has been unfortunate that many of the studies involving the vaccination of man have been poorly controlled and conducted and, in many instances, have been of little value in producing valid results from a scientific standpoint. However, this fact should not detract from the fact that there have been a number of relatively well-controlled studies reported, almost all of which showed reduced morbidity and mortality from tuberculosis in groups vaccinated with BCG when compared with nonvaccinated control groups. Among the latter reports should be mentioned those of Aronson and Palmer[43] involving the vaccination of American Indians, Ferguson and Simes,[44] T. V. Hyge,[45] and the report of Dahlstrom and Difs.[46] The studies reported by Aronson and Palmer and Ferguson and Simes have been criticized from several standpoints by some men, particularly on the basis of inadequate autopsy studies of the members of the vaccinated and control groups of Indians who subsequently died during the studies. It is generally acknowledged by most observers that the studies were well conducted from the standpoint of comparable groups as pertaining to age, sex, general health, period and adequacy of follow-up observations, living conditions, and chance of exposure to tuberculosis. It would, indeed, appear to be almost impossible to design and carry out a study involving the vaccination and exposure of human beings to tuberculosis over a significantly long period of time which would fully satisfy all of the rigid criteria considered desirable in the clinical laboratory where one deals with experimental animals and controlled environment. These obvious limitations on experimental studies in clinical medicine should

not, however, be considered justification for the complete acceptance of poorly conducted clinical studies.

Two mentioned reports warrant special attention. T. V. Hyge reported in 1947 an outbreak of tuberculosis arising from an infected teacher in a girls' school in Denmark. Among 105 tuberculin-positive students in the school, two cases of tuberculosis developed during a three-year period; also, among 106 tuberculin-positive pupils who had recently been vaccinated with BCG, there were two cases of tuberculosis, whereas among ninety-four nonvaccinated tuberculin-negative pupils, forty-one cases of clinical tuberculosis developed with one death. Although this outbreak of tuberculosis in the private girls' school occurred inadvertently, because of the knowledge of the pupils' previous state of health and state of tuberculin allergy and because of the comparable exposure of all the pupils to the same teacher under the same conditions, it fulfilled most of the criteria needed but frequently unobtainable in clinical research. Dahlstrom and Difs reported in 1951 the results of their studies involving the vaccination with BCG of 36,235 conscripts inducted into the army of Sweden during the years 1941 through 1944. This group of soldiers was shown to be comparable to a control group of 25,239 tuberculin-negative conscripts who chose not to be vaccinated. These authors found a ratio of 2.7:1 of clinical tuberculosis in their nonvaccinated and vaccinated groups. The mortality rate from tuberculosis in the two groups was 3:1, respectively.

The mass of controlled evidence supporting the efficacy of BCG vaccination, considered along with the much larger uncontrolled groups which are too numerous to mention, has led to extensive clinical use of the vaccine in the last few years. It is estimated that over 50,000,000 people have been vaccinated with BCG in the world today. In Japan alone it has been estimated that over 20,000,000 tuberculin-negative individuals have been vaccinated. BCG vaccination is being carried out to a large measure under the guidance of the "Joint Enterprise" which is made up of the Scandinavian Red Cross organizations. It has received funds from UNICEF (United Nations International Children's Emergency Fund) and has been aided by the World Health Organization. A widespread voluntary immunization program is going forward in Sweden and Denmark,[47] whereas in Norway[48] BCG vaccination is said to have been made compulsory for tuberculin-negative individuals in certain groups which have a high exposure rate to tuberculosis. In the United States, many physicians have been extremely reluctant to accept BCG vaccination of tuberculin-negative individuals, but it has been slowly accepted by some men as advisable on a voluntary basis for tuberculin-negative individuals in groups such as student nurses, medical students, workers in sanatoriums, and other groups where the chance of frequent contact with tuberculous individuals is great. The Committee on Medical Research and Therapy of the American Trudeau Society published a "Statement on BCG" in 1949[49] in which it was pointed out that under acceptable conditions BCG is harmless. It further stated that, like most vaccines,

the protection afforded is not complete and that, on the basis of studies in the literature, an appreciable reduction in the incidence of clinical tuberculosis may be anticipated when certain groups of people are vaccinated.

Why is it that BCG vaccination has been looked upon with disfavor by so many physicians in the United States? There are many reasons for this attitude toward BCG vaccination, some of which are attributable to deficiencies in the vaccine itself and some of which may perhaps be attributable to overly enthusiastic and unsupported claims made for the vaccine in earlier years.

BCG is a living avirulent bovine strain of *Mycobacterium tuberculosis* which has been subcultured for many years according to strict bacteriological standards. It is produced only in licensed laboratories where rigid standards of technique are maintained to ensure a relatively constant potency and absolute freedom from contamination. Since BCG contains viable bacteria, there are many who fear that a return of its previous virulence is still possible, despite the fact that no proved cases of tuberculosis in man have resulted from millions of vaccinations in the past twenty years. Some credence was lent to this uncertainty by the report of Vorwald,[50] in 1949, of the production of progressive tuberculosis in silicotic guinea pigs by BCG. Further studies involving BCG vaccination of silicotic animals may clarify this situation.

The instability of the vaccine has contributed to further just criticisms of the clinical usage of BCG. It is agreed by most investigators that the vaccine is stable for a period of only seven to ten days after the packaging of the product. The rate of death of the bacteria in the vaccine during this period of time varies with individual lots, and this rate is generally conceded to be excessive after ten days. Therefore, it is usually necessary to refrigerate the vaccine and distribute it rapidly to the physician who employs it, often by air transportation. Furthermore, various lots of BCG produced in different laboratories have been shown to vary considerably in their ability to convert tuberculin-negative individuals to the tuberculin-positive state, just as have various techniques of vaccination differed in this respect. The variance in potency of different lots of vaccine has led to variations in the dosages of vaccine recommended by various workers. In addition, the short life of the vaccine permits only limited potency testing on experimental animals and does not permit as thorough and exhaustive purity and safety tests of the vaccine before distribution as is desirable. This fact has increased the uncertainties of those who are reluctant to employ a vaccine containing viable bacilli. The severity of local reactions to BCG vaccination has also been a point of criticism in the past. Draining sinuses, regional adenopathy, and other complications have been found to be relatively common occurrences in some reports of vaccination. This problem has been at least partially controlled by the use of the multiple puncture method of application of the vaccine as recommended by Rosenthal.[51] This method of vaccination has been highly successful in converting tuberculin-neg-

ative children and adults to tuberculin-positive with an extremely low incidence of severe local reactions.

It is hoped that many of these handicaps may be overcome by the further development of freeze-dried (lyophilized) BCG which has been studied in recent years.[52] Birkhaug[53] in 1951 stated that with adequate adjustment of dosage the use of one-year-old dry or frozen BCG should prove just as effective as fresh liquid BCG. The dry or frozen vaccines would appear to be greatly superior since they may be stored for long periods of time without excessive loss of potency. This period of storage would also allow time for adequate control and purity studies to be conducted before the release of the vaccine for clinical use. However, the future clinical value of lyophilized BCG has not been fully assessed at the present time.

A further objection to the employment of BCG, which has frequently been cited, has been the unknown duration of immunity produced by vaccination. However, the actual duration of acquired resistance following many immunizing procedures used in clinical medicine today is often uncertain and differs in individual patients. It is believed that the duration of immunity following vaccination with BCG may vary from months to several years, and most workers in the field feel that only the persistence of a positive tuberculin reaction following vaccination signifies continued acquired resistance in that individual. The length of time that a patient remains tuberculin-positive, however, will depend somewhat upon the concentration of PPD or old tuberculin used to test that individual as well as on the criteria used to determine whether or not the tuberculin reaction is positive. It should be realized that the character and intensity of tuberculin reactions following BCG vaccination differ from those observed following natural contact with tubercle bacilli. Rosenthal[54] suggests testing with 0.1 ml. of 1:100 old tuberculin (1.0 mg.) if weaker dilutions fail to produce a positive reaction following vaccination. If this concentration of old tuberculin fails to produce a positive tuberculin reaction, revaccination is recommended. Attempts are being made in vaccination programs currently being carried out in Europe to better determine what concentrations of old tuberculin or PPD should be used for tuberculin testing before and after BCG vaccination.

Some clinicians still contest the contention that BCG actually stimulates any antigenic reaction when injected into man. It is beyond the scope of this paper to attempt to discuss further the voluminous literature which has been published through the years on this controversial subject. The literature dealing with this subject and, indeed, with all of the objections that have been raised to the clinical use of BCG has been well summarized by Myers.[55] It is easily observed while studying the literature on the subject of the efficacy of BCG vaccination in man that at times the views presented are prejudiced in favor of or against this highly controversial vaccine and that at times such prejudices have influenced what facts are presented. Claims have been made that the reduced morbidity and mortality rates from tuberculosis in some areas

and countries in recent years have been due to the extensive vaccination of tuberculin-negative individuals with BCG in those countries. However, it has been pointed out that full credence cannot be given to the belief that the reduction in tuberculosis mortality in countries such as Denmark and France, where BCG has been widely used, has been due primarily to the vaccine,[56] for the mortality from tuberculosis has declined in countries such as Iceland and the United States in the past twenty years without the utilization of BCG vaccination. If broad usage of BCG had been undertaken in these latter countries during this period, the reduction in mortality from tuberculosis might have been erroneously attributed to this procedure. It must be stated that the vast majority of the clinical studies reported involving the vaccination of man with BCG have indicated a reduced morbidity and mortality rate from tuberculosis in the vaccinated groups. Comprehensive reviews of the antigenic properties of BCG may be found in the writings of Irvine,[57] Anderson and Palmer,[56] King,[58] and Edsall.[59]

Enthusiasm for the widespread employment of BCG for all tuberculin-negative people has led, in the past, to the recommendation by some men that BCG be used on a wide scale in all countries with little regard for the magnitude of the problem of tuberculosis and the facilities for its control in individual communities. This overly enthusiastic and optimistic attitude has led to the just criticism that in many areas where tuberculosis is a relatively minor problem and is well controlled by existing health measures the conversion of a large portion of the population to a tuberculin-positive state by BCG vaccination would deprive the physician of the value of the tuberculin test as a diagnostic aid. It has further been stated that the widespread usage of BCG would greatly detract from the excellent and successful public health measures that are being employed, since the public might lose interest in aiding in case-finding and the prevention of tuberculosis if it is believed that a "vaccine which will prevent the disease" is available. If such an attitude were to prevail, it would indeed be unfortunate, since the resistance which may be produced by BCG is a relative rather than absolute resistance, just as is the case with most other vaccines.[49]

What course can the practicing physician follow when he is consulted concerning the question of the advisability of BCG vaccination in the prevention of tuberculosis? It has seemed advisable to many workers in the field to recommend vaccination for tuberculin-negative individuals who are faced with the prospect of living or working in an environment where there is a high incidence of tuberculosis and where exposure to active tuberculosis is considered likely.[60] As mentioned previously, BCG vaccination is being offered at many medical centers to tuberculin-negative nurses and medical students since the incidence of tuberculosis is much higher among medical students than among similar groups of young adults in the general population. Many Indian reservations in this country are said to have an extraordinarily high tuber-

culosis morbidity rate and inadequate medical facilities for the care of those who have active tuberculosis. There are numbers of penal and mental institutions throughout the world where the same situation still exists. In our present state of knowledge concerning the mechanisms of immunity to tuberculosis, it would seem advisable to utilize all measures available, including BCG, to help decrease the incidence of tuberculosis in such situations, meanwhile continuing every effort to control tuberculosis through the currently employed successful and proved measures of prevention, case-finding, and treatment.

SUMMARY

A brief review of antituberculosis vaccines has been presented with emphasis on BCG. At the present time BCG is the only antituberculosis vaccine which has been shown to be effective. Current concepts of BCG vaccination have been discussed. It has been recommended that BCG vaccine be used for tuberculin-negative individuals living or working in an environment where there is a high incidence of tuberculosis.

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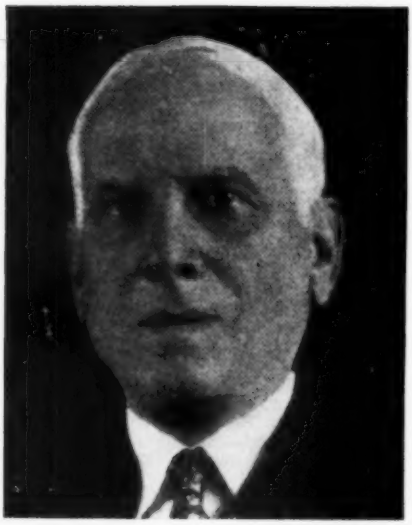
Pediatric Profiles

Henry Dwight Chapin

(1857-1942)



"The life of the child is the most valuable asset of the nation."

HENRY DWIGHT CHAPIN, The Puritan, was the first socially conscious American pediatrician. As early as 1887 he was writing to the effect that society must strive to "atone for its fearful inequalities, not by division and alms, but by strengthening the weak for a more successful effort." In his late maturity the key to all his endeavors centered on the note that "the home is the source from which all lasting improvement [of children] must come."

Dr. Chapin presented to the world a complex personality. The puritan conscience is not on all occasions a comfortable companion. The personal security that comes from a sense of righteousness seems always to end in the conviction that into each man's hand is given the ultimate shaping of his career. Whatever the work, he can grasp it by its bigness or its pettiness, according to his nature. There is no comfort offered in a softness that is called philosophy.

The making of a puritan demands the fortunate—or unfortunate, according to one's personal point of view—conjunction of diverse factors. Inheritance and family training have their uncharted rolls, but other conditions equally vague play their part. Freedom of inquiry, the right to speak out in favor of unpopular programs, and, above all, an impelling cause serve to mold the man into a crusader who is convinced that ideas are the primary purposes of life. There is a good deal of stoic philosophy in the puritan make-up. Emotional reactions, good or evil, funny or tragic, must be hidden from friend and foe alike. Duty is a command that cannot be lightly set aside.

There were many duties in Dr. Chapin's life, among which were the important ones of being true to one's self, of ameliorating the conditions under which the less fortunate live, of combining sanity with philanthropy, and of avoiding hard-handed indifference on the one hand and the even worse bane of irresponsible quixotism on the other. The resulting conflict

between desirable ideals frequently ended in the charge that he was "changeable."

Dr. Chapin accepted as a personal responsibility the social maladjustments that he saw around him. He did this modestly, realizing that he could not do much by weight of numbers and that he must make his effort as a pioneer and by sowing the seeds for a later and greater effort. Out of the conflict between what "is good" and what is feasible emerged a doctor who was that rarely understood individual, the practical idealist. In an hour he was by turns irritable, brusque, and deeply tolerant of human weakness; and the rigid moralist contradicted by forgiving optimism.

Dr. Chapin possessed a puritan conscience by right of inheritance. He was the direct descendant of that deacon, Samuel Chapin, who took the freedman's oath in Boston in the year 1642. The old deacon was already a man of worth in the town of Dorchester. In this same year he moved his family and his religious principles westward to the frontier, settling on the outskirts of what is now the city of Springfield, Massachusetts. A hundred years passed and his descendants were again on the move westward, going for the most part into Central New York State. Dr. Chapin's grandfather was one of these migrants. There was no promise that paradise was around the corner, for the Chapins held firmly to the conviction that the Lord helps those who help themselves. The home and the family were the centers around which their life revolved. They knew good and evil, and became virtuous by choosing the good.

Dr. Chapin was born in Steubenville, Ohio, on February 4, 1857. He was the first-born child born into a family devoted to religion and education. His father was a Congregational minister with leanings toward the Unitarian doctrine. The family wandered, as is the case with many minister's families, to Trenton and to Princeton in New Jersey, and finally settled down in New York City, where his father established in 1870 the fashionable Chapin Collegiate School for boys.

The school offered an old-fashioned education. There was no pretense of preparing a boy for anything except the learned professions and the importance of living a righteous life. Nonconformity was not encouraged. There is no evidence that Dr. Chapin failed to conform at any point through an undistinguished scholastic career in the preparatory school, in college (Princeton), and medical school. He must have learned a few things well, for there is no record of difficulties with passing grades or with disciplinary actions. It is, perhaps, an act of wisdom to hastily add that the students of that day were well grounded in a few of the essentials of living and that many of them, in time, achieved notable successes as men endowed with inquiring minds.

Dr. Chapin entered The College of Physicians and Surgeons in 1879, and was graduated two years later. We have his word for it that on present-day standards it was a poor medical school. It was, in fact, a proprietary school. At the end of the year the owners divided up the profits which, in turn, were dependent upon the number of students enrolled in the front office.

The medical students of that day attended or were absent from classes on their own choice. It was a practical possibility for a young man to graduate without attending a lecture during the two years that he was supposed to be in attendance at medical school. The curriculum left nothing to the imagination. Lectures were cut and dried, dealing for the most part with traditional and sacred material that had been handed down through uncounted ages. There were a few honorable exceptions, but most of the professors gave the same lectures year after year with no change in the content. The one thing that was common to all medical teaching of the times was that the physician must keep "a masklike face" in order to avoid "a quick and bad effect on the patient." Dr. Chapin never wholly escaped from this teaching. To the end of his days of practice the father and mother commonly had to interpret Dr. Chapin's opinion of the state of their child by the inflection of his noncommittal grunt.

A few laboratory courses were available to the student on the payment of a special fee. It was about this time that Dr. T. Mitchell Prudden established at P. & S., in a small cubbyhole at the top of a flight of stairs leading out of the main assembly room, a laboratory. The laboratory contained a microscope and a few simple utensils for growing bacteria and cutting tissue sections. The observant student—and they were few—might at about this time have noticed the youthful Drs. William Welch and Francis Trudeau hastily scurrying up the stairs to witness a demonstration of a new bacterial discovery. A short distance away at Bellevue Hospital, where Dr. Chapin served a term as intern, another young intern, who in time was to become a world-famous surgeon, was discovering a principal duty of going out on Second Avenue to steal hair from passing horses' tails for suture material.

Pediatrics in 1885 was the unwanted foster child of internal medicine. The subject was not taught in medical school except as an unescapable incidence of general medicine. The physicians of the period unashamedly confessed that "granny" knew more about babies than they did. Babies commonly were regarded as wet, smelly bits of humanity who lived or died, as the case might be, under the providence of God. The doctors who attempted to confine their practice to small children were disrespectfully and rather scornfully called "baby doctors." As a matter of fact, pediatrics for more than a score of years commonly traveled under the pseudonym of diseases of children. It was not until the 1930's that pediatrics became a commonly accepted word to define the specialist in the care of children.

Dr. Chapin began the practice of medicine in 1885 on the edge of the slums of the West Side of Manhattan Island. It is probable that a permanent Medical Practice Act had not been passed in New York State. The state of Illinois set the pattern in 1877, but the other states were slow in following the example. In most areas a certificate from any medical school diploma mill was sufficient evidence that a student was prepared to practice the art of medicine. A year in the medical centers of Europe set the young doctor apart as an expert.

The infant mortality rate for New York City in 1885 was 273 per thousand. The slum area in which Dr. Chapin began the practice of medicine was a noisome and evil district. Its water front was lined with docks and slaughter houses. Cow sheds accompanied every brewery where cows with rotting tails were fed the discarded beer mash. The thin, dirty milk from these starving animals furnished most of the food for the neglected infants of the district. Dilapidated tenement houses filled every block. Bath tubs, if by chance they were present, were regarded as handy receptacles for the storage of coal. The poorest of the poor lived in broken-down inner tenements. Running water and toilet facilities (privies were still common) were placed in inconvenient locations in the hall or even downstairs at the street level. Bedbugs, lice, and rats had the free run of every home. The stench that pervaded the district made it a place that nice people avoided.

Vice, poverty, and ignorance was the accepted privilege of the swarming mass of humanity that had to live in the district. Drunkenness was nearly a universal habit. Venereal disease was an unfortunate accident which everyone had to put up with. Gangs of hoodlums, or worse, roamed the streets. All in all, it was a hard world for those born in the shadow of it.

Born with a good deal of New England granite in his soul, the youthful Dr. Chapin refused to accept or even to listen to councils of despair. Contrary to personal advantage, and even to inclination, he began within a period of half a dozen years to pioneer ideas of better housing, of less poverty, of more education, and of a better religion. He developed the queer notion that "the life of a child is the most valuable asset of the nation." He preached that the physical conditions of great areas of the city were designed to defeat every altruistic effort of the physician in favor of a better life for children.

The Puritan heritage got the better of his inner urge for conformity. He had to accept a personal responsibility for forming the ideals and fixing the standards that should rule in offering aid to submerged people. Later, as he approached the end of a long life, he was to write that everywhere "I saw so many people who are physically, mentally, and morally unequipped for life that this [social problems] seemed a fundamental topic of physicians and reformers to consider." The fashionable thing for the privileged few (the religious, the educated, the prosperous) was to ignore the conditions in which "the other half live" on the general principle that what you do not see simply does not exist. If some fortuitous accident called attention to the matter, the reaction was a fear that some unlucky chance of fate might precipitate you yourself into this miserable abyss of squalor and misery. This ignoring of a situation at your back door was proudly called "being practical."

It is the teacher, the writer, the journalist who form the minds of a people to love the truth and honor the "good" man. Dr. Chapin by instinct was primarily the teacher, the writer, the moralist, and perhaps the journalist. As time passed, the central core of his personal philosophy seems to have been expressed in the

sentence that "a joyous child was the answer to most [of the] questions that plague the doctor and the family."

The successful physicians of the period occupied a whole house with their offices located on the ground floor. The telephone did not disturb their days or nights. It was not many years before Dr. Chapin bought the "front door knob" of a house on West Fifty-first Street just east of Sixth Avenue (now a part of the grounds occupied by Rockefeller City). This moved him into a more comfortable neighborhood and on the edge of the world of fashion. He did not move again until the time came for his retirement from the practice of medicine.

We have no authentic picture of the student or of the young doctor at the beginning of his career. By the time he had reached middle age he was an attractive figure of a man. He stood about 5 feet 10 inches in height, with a tendency to appear stocky. He carried himself erectly and with a determined air as if he knew exactly what he was going to do next. His hair, always parted smoothly in the middle, was snow white. His eyes were blue with a quality of gaze that suggested that they missed nothing that went on within the range of their vision. The complexion was clear with a touch of color over the cheekbones. In a period when a beard was almost the trademark of the physician, he went about his business freshly shaven. In moments of concentration he had the habit of nodding his head slightly toward the right as if to emphasize the point that he was making. Given a flowing cape, a conical hat, and a Bible in his right hand, he could have sat as the living model of St. Gauden's notable statue, The Puritan. In Dr. Chapin old Deacon Samuel Chapin authentically walked the streets of New York City over a period that exceeded a half century.

The paradox of the righteous Puritan nature is that they enjoy success and the good things of life. Dr. Chapin was no exception to the rule. He liked vintage wines but frowned on strong drink. Nearly every summer he made the conventional tours of Europe. An invitation to tediously long dinners in the homes of fashionable wealth flattered him. The violin became him and he played the instrument with some skill. In fact, he was the authentic image of the safe, moderately successful mid-Victorian gentleman. With no change at all he could have stepped into a Christy or Gibson cartoon, or posed as the true hero of a Richard Harding Davis story. The superficial observer must have found it difficult to conceive of this nice gentleman as a man who insistently demanded for himself the right of "freedom of inquiry," and as a person who harbored horrifying ideas about the needs of uncomfortable people. After all, the status quo was a sacred concept of the times and was to be disturbed only at the cost of personal peril.

The ghost of Dr. Chapin's Puritan ancestors drove him relentlessly into the roll of the practical idealist. The idea that unified his life work was the "right of every child to be placed in an environment that favored optimum growth." We can ask the question of what turned Dr. Chapin toward pediatrics without receiving the shadow of an answer. Perhaps the

answer is as simple as that he had an inborn love of children. Still, we have to remember that in those days the "baby doctor" was not commonly considered as presenting evidence of strong virile manhood. Infants by common consent were left to the sentimental womanish type of doctor.

In 1885, as has already been hinted, the general practitioner received practically no instruction in the medical school in the care of infants and children. Their ignorance was abysmal and was self-confessed. About this time a new hospital was on the way in New York City—The New York Post Graduate Medical School and Hospital. It was proposed to set up in the new hospital an independent and integrated service for the care of infants. The Babies' Ward was the evidence that this idea was in being. In addition to this service, it was proposed to teach pediatrics in the clinic and on the wards on the same basis that other subjects in the school curriculum were taught. Dr. Chapin became, about 1885, the Chief of the service. Space was provided for the children's clinic and for the wards. The budget took care of the patients but never offered the doctors in attendance even a token salary. We can today wonder how the unit was staffed, for the demands of teaching and attendance became an increasing burden with every passing year.

There are periods in pediatric history when half a century makes more change than the ages that went before, or perhaps, that will follow afterward. This was true of the fifty years immediately following 1885. The tyranny of superstition, indifference, and ignorance came to an end almost in a matter of months, and was replaced by a time of activity and of free inquiry. No hallowed belief was spared and no traditional racial custom dealing with infants failed of examination. The kindest thing that we can write of the preceding centuries as they dealt with children was that the teaching was ancient and quaint, and that it dealt with a decaying rather than a growing child world.

Each man's mind has some peculiarity that distinguishes him from all others. Most men are what they are, good or evil, useful or not, by their education. Heritage and education both made the young Dr. Chapin ask what the doctors as a group could do for the preservation of child health. He noticed in the early days of his practice that the poorly nourished and feeble child rarely, if ever, grew up into an adult with "a sound mind in a sound body." Children, in his opinoin, could not be put into the herd and driven by the whip.

Learning is the least part of wisdom, for wisdom lies in the ability of managing the business of living with foresight. And so he began his teaching, not with a list of abstract facts, but with the demonstration of living cases. The first thing was to fill the gaps in the knowledge of the average physician so that he could better deal with the childhood problems placed at his door. If the doctor was not educated, he could not hope to direct the lives of children into paths of health and happiness.

Dr. Chapin's Monday demonstrations from 12 to 1 o'clock were attended by a phenomenal number of general practitioners of medicine. Their numbers by 1900 rarely fell below one hundred and often ap-

proached two hundred. He took a selected number of students on ward rounds. Questions and discussion were encouraged. This method seemed to him to be so natural a way of teaching child care that to the end of his days he never sought credit for being one of the early men to introduce case teaching as a wise method of learning medicine.

"Happy children not only get well more easily but more certainly than unhappy, lonesome children." Out of this concept the wards began to take on color and were in a constant state of cheerful disorder. In the period of the "prophylactic baby" this section of the hospital was the despair of the head nurse who agreed that it was a pleasant place in which to live but was no real hospital. In order to foster a closer contact between the home and the wards, a weekly visiting period for parents was established at a time when father and mother, more often than not, were not allowed to see their child from the time he passed through the admitting room until he was discharged as cured, improved, unimproved, or dead. Many a pitying nurse spent her spare moments holding a child up to a window so that the parents could look at their child from the sidewalks across the street.

Another innovation hard to explain, with the ideal in mind that the "doctor must keep a masklike face," was the early custom of having an hour when a staff physician was available for an interview by the parents. The doctor assigned the task had a mixed hour of glory and blame. In the face of abuse or praise he was instructed to remain calm and sympathetic. "Remember we have no cases on this service but individuals that are the center of ambition and love in a home. Treat these children as you would like your own treated if some misfortune placed him here."

Dr. Chapin never gave it a name, but from the first he knew by a kind of instinct that no sick or well child could be successfully directed medically without a complete knowledge of his environment. In this more enlightened age we call it treating the "whole child," or, if we seek to bewilder the lay public, we name it psychosomatic medicine. The thought is not very new. In any event, Dr. Chapin established in 1891 in the babies' wards a hospital social service organization. The purpose was to relate the child isolated in the wards with the family back home. It seemed to Dr. Chapin that it was "the right of every child to be placed in an environment that favored optimum growth." Obviously the right could not be offered in the hospital unless there was full knowledge of the home from which the child came.

Discipline was considered to be a growth and an educational pattern that depended more often than not on the home pattern. Education was regarded as essentially a religious experience—not sectarian, but religious in so far as its purpose was a decent and good life. "Faulty conditions in the home inevitably defeated all efforts to improve the life of children at every social level."

A wholesome milk supply became a major interest of Dr. Chapin during the 1890's. Certified milk* intrigued him as an evidence of what could be accomplished if milk was properly handled. However, it was too costly —and always would be—for the aver-

age family. What he sought was a safe, wholesome milk at a price that the masses of the people could afford. He climaxed his efforts with a book, titled *Milk*, that became, for a brief time, a handbook for all public health officers interested in obtaining a safe food for the children of their communities.

A system of infant feeding that was familiarly labeled as "percentage feeding" received Dr. Chapin's qualified support. He was convinced that any system of infant feeding that could qualify for universal acceptance must be simplified to the point where the average mother could make the mixture in her kitchen with the minimum number of errors. In any event, it was an erroneous assumption to suppose that any system of skimming and dilution could duplicate mother's milk, for milk was a biological fluid. No matter what modification of cow's milk was made in the home, the end result was still cow's milk.

Calorie feeding in Dr. Chapin's estimation had a certain value as a measure of energy, but it told nothing about the mixture as to its suitability as a food for infants.

With all these various irons in the fire, Dr. Chapin's attention to his hospital service never wavered. The conclusion in the course of time became fixed that the wards were no place for small children and infants. Special situations of diagnosis and treatment made such facilities necessary, but the objective of getting the children into homes in rural or semirural surroundings should not be neglected. As soon as it could be safely managed, children should be moved into an "optimum environment." Out of this idea there grew the Speedwell Society whose objective was to place convalescent and neglected children in supervised homes in the country. Dr. Chapin had an enduring faith in the therapeutic value of mothering the sick infant and small child.

At the midcentury of his life Dr. Chapin had apparently completed his major tasks. "Pioneering and the sowing of seed for a greater effort" were for youthful men with leisure and an urge to reform the world. To be sure, he wrote a textbook and various papers, but his heart was not in the work.

Dr. Chapin reached middle age before he married. The new mistress of the home was pretty and a gracious hostess. She was a Delafield, a niece of the great Dr. Delafield. People liked to be entertained in their home. He took comfort and pride in his wife and in all her activities. All that seemed to be ahead of him was a growing practice that with attention might easily become a wealthy one. Outwardly the temptation "to make a new and greater effort" had disappeared in the haze of a happy home and the promise of prosperity.

And yet this man, who had so much, was to repeatedly observe in the twilight of life that "I had to wait until I retired to find my true

*Much or perhaps all the credit for the idea of a "certified milk" must be given to Dr. Henry L. Coit of Newark, New Jersey. Dr. Coit became convinced of the feasibility of a clean milk of superior quality through his interest in a dairy farm that he built up in Northern New Jersey. The time involved became so costly that he interested a group of wealthy men in the idea. They bought the farm, continued Coit's policies in the collection and care of milk, and finally organized the Walker-Gordon Company. So far as I know this was the first practical effort to supply a clean milk of superior quality for the general public. The demonstration was successful, but had the defect of being too costly and too complicated for general acceptance.

life work." The happy marriage had one facet of disappointment. There were no children, and they both wanted and loved children.

It began almost by accident. On one spring morning in 1912 the morning papers carried a spread on the front page of the finding of a baby girl wrapped in newspaper under a Central Park bench, by a policeman on his early morning rounds. Dr. and Mrs. Chapin gathered the unwanted baby into their home. The nursery on the top floor of their home was at long last occupied. After a deal of reflection and heartbreak, Dr. Chapin decided that he was too old to assume the responsibility of raising a baby daughter to maturity. A superior home was found for the unwanted—and now wanted—waif. It was the beginning of a new crusade.

The top floor of their home was immediately expanded into a nursery with half a dozen cribs. The space was soon all occupied by unwanted babies. A gain in weight and the bloom of health soon made them wanted children. Dr. Chapin observed that a pink ribbon, fresh linen, and attractive surroundings made all the difference in the world in the matter of the future destiny of these unwanted infants. They found superior homes.

In 1917 the doctor and his wife made a trip to the West Coast and back. They stayed each night in a home in which they had placed a child. We are allowed to suspect that there was never another similar trip made by a man and wife who wanted children and who, on being denied the privilege, made all neglected infants their own. They found their work good. In the course of time the two of them together found a place for wanted children in nearly two thousand homes.

The experience of placing unwanted children in homes that wanted them confirmed a long-held opinion in Dr. Chapin's mind. He was to write, as a final conclusion, that the institutional care of children "is wasteful of child life, wasteful of efficiency and character because they do not give an experience to the child in natural family and neighborhood relationships, or give an opportunity for the development of self-reliance and self-direction."

"I never made from the practice of medicine more than $12,000 in any one year; and my largest consultation fee was $1,000." Of course, the making of a large income from practice was never more than a secondary purpose in Dr. Chapin's professional career. He was always a careful man, but he never was a paltry one. Something can be said for the powers of thrift and compound interest in the fact that he left an estate of nearly $200,000, earned by personal sacrifice and hard work. Like many another man he early made the discovery that his obit, as is the way with obits, related to what must have appeared to be the less important things about himself. He valued security, but he willingly placed it in the balance against the right of freedom of inquiry and of the greater right of freedom of action.

The wrath of the Almighty was never so many words to Dr. Chapin. He knew that ideas do not keep. The new custodians of an idea have fervor, live for it, and, if need be, die for it. The inheritors of the idea, perhaps now strong and successful,

do not inherit the fervor, so that the idea all too commonly settles down into a comfortable middle age.

The social climate of a generation can change with the passage of time. Dr. Chapin lived to see his rights of children gain universal acceptance—and those rights were the right (1) to live; (2) to a mother; (3) to a home; (4) to play; (5) to be happy! (6) to be trained to a proper development.

Like many another man who lives by faith, Dr. Chapin was often worsted in an argument, but he possessed the secret of a "good life." He sacrificed much, but finally the bitter turned to sweet and he could say that " it is well as it is."

Dr. Chapin lived to be 85 years old. The final chapters were years of distress and pain, spent for the most part in bed. The cheerful gossip of his beloved Century Club became a dim memory. He enjoyed the rare visits of "his boys," now become prosperous practitioners of medicine. The lonely hours left much time for reflection.

Chiefly, he was pleased with the thought that his life had not been a Ferris wheel journey that finally deposited him at the gate by which he had entered upon his career. After all, his accomplishments were many. His seemingly forlorn efforts at pioneering had borne fruit, and pediatrics in his life period had made startling advances. He had seen many join his ranks so that the revolution of the 1880's and 1890's had become the platitudes of 1950.

He was grateful that he had never made pets of children but had treated them as rational and responsible people, his equal, having feelings that deserved the same consideration that he might show an adult. And the children had responded, for they came to him naturally in confidence and trust.

To be sure, there were no monuments honoring his name. In his hours of wisdom he was glad that this was so, for he had often noticed that monuments had a way of losing their usefulness before the final stone was laid. The excellencies of today's needs were not, in his opinion, a sound reason for continuing the aid after the need was ended.

As he reviewed his years it seemed to him that he had led a good life, with the reserves that were proper to the Puritan spirit.

They say that Dr. Chapin is the forgotten American pediatrician. Perhaps this estimate is true. Simple, honest men with common-sense answers to the problems of their day are easily forgotten. The truth which is unacceptable today becomes the commonplace of the tomorrow. The worst does not last. Dr. Chapin's enduring monument is that he found many forgotten children and that he placed them out in the open where God's sun could touch them.

Dr. Henry Dwight Chapin died in the early morning of June 28, 1942. He had had his day and it had been a good day.

Marshall Carleton Pease

Comments on Current Literature

LIVER CHANGES ASSOCIATED WITH FERROUS SULFATE POISONING

THE hazards of medicinal iron, notably ferrous sulfate, as a source of poisoning, particularly in young children, have been emphasized in recent years in numerous published reports. While the clinical manifestations have been well recognized, the fundamental pathogenesis of iron intoxication is not entirely understood. The treatment advocated has been largely symptomatic, or has been based on impressions derived from clinical observations of therapeutic trials, such as the use of BAL (British antilewisite, 2, 3-dimercaptopropanol, or Dimercaprol),[1, 2] or the use of mixtures of thiamine hydrochloride, nicotinamide, riboflavin, tocopherol, and methionine, therapy suggested by the possibility "that the iron acting as a heavy metal, may combine with –SH groupings and thus interfere with oxidation. The tocopherol is given in an effort to reduce the oxidative requirements of the cells, and the methionine as a source of –SH groupings and as protection for the liver."[3]

In a recent issue (Dec. 16, 1954) of the *New England Journal of Medicine*, Luongo and Bjornson[4] report pathologic changes in the liver in three fatal cases of ferrous sulfate poisoning in human subjects and in experimental animals, the experimental study being prompted by the need to verify the hepatic lesions observed at autopsy in the fatal human cases. A survey of the literature revealed that hepatic changes associated with ferrous sulfate poisoning have been recorded and discussed to some extent. The hepatic changes observed, however, varied widely from cloudy swelling of liver cells to complete necrosis. The lack of consistency in these reported pathologic findings influenced the authors to describe in detail liver changes which they consider characteristic of the condition.

The three human cases reported by them[4] were three infants, aged 16, 18, and 12 months, respectively, all of whom died within a period of from somewhat less than twelve hours to thirty hours following ingestion of lethal doses of medicinal ferrous iron. Autopsy findings, reported in detail in all three cases, indicate that the liver is the seat of significant histologic change. In the first infant, 16 months of age, the cells in the portal areas had disintegrated almost completely, and those in the central portions showed severe cloudy swelling. Of considerable interest was the presence of a fine deposit of iron, definitely periportal in distribution. In the second case, a child of 18 months, the hepatic changes observed in tissue taken at autopsy were regarded as striking. "A narrow zone of necrosis surrounded all portal tracts. In these necrotic areas the size of the cells was markedly diminished, and the cytoplasm compressed, with loss of nuclear and cytologic detail in general."[4] Specific staining for iron revealed a deposit of finely dispersed iron in the necrotic periportal areas. Autopsy studies in the third case, child 12 months of age, disclosed patchy areas of hemorrhagic necrosis, most of which surrounded the portal tracts. In this case, specific staining methods showed only "a barely perceptible deposit of iron-staining material in necrotic areas."

An experimental study of ferrous sulfate poisoning was undertaken in

rabbits, all factors being kept constant except variation in dosage of ferrous sulfate fed by stomach tube. Animals on the larger doses died within a few hours following administration of the ferrous sulfate. Survivors on smaller doses were killed at intervals varying from one to thirty-five days. Periportal involvement of liver cells was a constant feature in all the experimental animals. Depending upon the dosage and time after ingestion of iron, the pathologic findings varied from severe hemorrhagic necrosis with infiltration of polymorphonuclear leukocytes to slight degrees of periportal proliferation of fibrous tissue with minimal infiltration of small mononuclear cells. The presence of periportal proliferation of fibrous tissue and of fine diffuse hepatic fibrosis in animals surviving for from five to fourteen days after ingestion of iron suggests that sublethal ferrous sulfate poisoning might result in a more chronic form of hepatic involvement.

On the basis of their observations in three human subjects and in experimental animals, the authors conclude that in acute ferrous sulfate poisoning the outstanding pathologic change consists of a hemorrhagic periportal necrosis, regarded by them as a characteristic type of "zonal necrosis."

This timely report by Luongo and Bjornson not only serves to re-emphasize the real dangers of serious poisoning with iron products, but also contributes significant information concerning the pathogenesis of the process. In a provocative discussion the authors raise the question of the possible dangers of iron ingestion either in food or in therapy, and of the effects of large doses of iron, particularly in patients with abnormal hepatic states. They mention, likewise, the possibility that prolonged iron ingestion, even in moderate dosage, might lead to a pigmentary type of cirrhosis. A pigmentary cirrhosis of this type has been described in the Bantu of South Africa.[5]

Reports such as these are thought-provoking and serve to remind the physician that iron preparations, valuable as they are when indicated, can still constitute a real hazard if distributed without careful evaluation.

RUSSELL J. BLATTNER

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Correspondence

[The following are excerpts from a letter, discussing the editorial on breast feeding, from the wife of a scientist, which was too lengthy to publish in its entirety.]

I should like to take issue with the first statement in the editorial. I am not at all sure that breast feeding is declining. I think that the circle has become complete—fifty years ago the woman who was well-to-do would turn her baby over to a wet nurse and go about her activities, and the poorer woman had to nurse hers if it was to live. Today, the poorer woman knows how to pour canned milk into a bottle, add a little water and sugar and give it to her baby. And the well-educated woman, who feels that breast feeding is important, is anxious to nurse her child—and does.

My husband and I have three children, aged 2, 4, and 7½ years. I nursed each one until he or she was nearly a year old. My own attitude toward breast feeding has been influenced by several factors. I was reared to think of it as the natural thing for a mother to do, not as an "animal-like" thing, and I always expected that that was what I would do.

Why should a mother nurse her baby? You ask, "Is it worth the bother?" I say "yes." First of all, you have a happier baby—none of this fussing to see what will agree with him. He likes his food and is anxious for it.

The second, and a very important, reason for nursing babies is that it is so simple. No bother at all. No bottles, no trying to stir powders into water when they do not want to go into solution, no measuring, no cooking, no sterilizing, no carting bottles wherever you go. The baby has his food wherever and whenever he wants it, with no effort whatsoever by the mother. As a matter of fact, she will have even more milk for him if she lets her house go and watches television instead. It is the lazy lady's way of feeding a baby.

Many laymen and doctors alike point with pride to the rapid gain in weight of babies on formula. But is that a valid criterion of the superiority of bottle feeding? Tests made with animals have shown that those fed ad libitum grew faster and were fatter, but also had a shorter life expectancy than those on a normal intake.

Some women feel that they will lose their figures if they nurse their children. A mother's breasts are enlarged and heavy long before she ever has her baby, so I do not think it can be blamed all on nursing.

And then there is the feeling that nursing a baby is sort of "low-brow." With some people it is almost a feeling of revulsion—that it is an animal-like act. My blunt comment is, "What can be more animal-like than conceiving the baby?" Actually, I think this is one of the greatest deterrents to breast feeding that there is. And this is where education could do a lot.

Hospital personnel are busy, of course, but if a woman is discharged on the fifth or even the seventh day, it is not too late to start nursing her baby when she gets home. She will have sole control of him then, and can pick him up as often as she likes. Rooming-in may be a good idea for apprehensive primiparas, but personally I look forward to the rest—I'll have enough baby when I get home. (Doesn't that sound hard-boiled?)

One of the most important factors—perhaps the most important—is to have help at home. A new mother who wants to nurse her baby MUST NOT be overworked. If the living-room floor is littered, the dishes undone, and the beds unmade, so what? You are nursing your baby, and that is the most important thing to do for these few months. You can dig in and clean the accumulated dirt out next month. Your husband can jolly well do the dishes when he comes home from work. But you—you are going to be placid, and not rushed, and if friends come in and see what a sloppy mess you are, you are not going to worry. I realize that this

is a lot easier to say than do—but I have done it. With my third baby, if things were rushed, I found that I could just go in the bedroom with the baby and by sheer will power (of which I do not have much) force myself to relax and unkink and not even notice the uproar in the other part of the house. It can be done.

I do not expect I am what you call a "natural nurser." I had to complement breast feedings for the first six weeks with my first-born, but not with the others. You hear a lot of rhapsodic talk about the great joys of nursing a baby—how it is such a thrilling performance. I personally think that is overdrawn. But it is a nice experience—there is a closeness and a warmth and a feeling that you are giving your baby just exactly what is best for him. That makes it worth while.

C. P. T.

Dear Dr. Hill:

I was very interested in your editorial on breast feeding.

I enclose a reprint of a recent investigation which I carried out in Belfast on the incidence of breast feeding, which proved to be disappointingly low. It was interesting that we did not find any significant difference in the success of breast feeding between babies born in hospital and at home, which has made me wonder whether some of the factors that we have blamed for failure for breast feeding, e.g., the impersonal atmosphere of the hospital antenatal clinic and the rush to get the mothers home after the babies are born, are as important as had been thought. We do keep most of our mothers in the Royal Maternity Hospital for ten days whenever possible (i.e., unless there is very great pressure on the available beds) and I would be very unwilling to reduce this period.

My own feeling about breast feeding is that success or failure is primarily a matter of the mother's approach, which in its turn tends very largely on such outside influence as the attitude of her mother or mother-in-law, the advice and interest shown by doctor or midwife, and the "Tribal Custom" of her district!

The main advantages of breast feeding are, in the case of hospital patients from poor homes with few facilities for hygiene, and possibly little interest for hygiene, that it reduces the risk of infection considerably, and, in the case of the mother from a good home, with a good knowledge of hygiene, that it is very much less trouble than artificial feeding when proper precautions are taken with the latter.

One cannot argue away the very obvious fact that many babies thrive and develop very well on artificial feedings, and I think it is a waste of time to tell a mother that breast milk is the best food for the baby and leave it at that.

I feel, myself, as a clinical impression, that breast-fed babies are healthier, but it is next to impossible to obtain statistical proof of this.

I shall be very interested in further reports in your JOURNAL and any steps taken in the United States to increase the incidence of successful breast feeding.

W. A. B. CAMPBELL, M.D., M.R.C.P., ED.

Dear Dr. Hill:

I greatly enjoyed your editorial on "breast feeding." It seems to me, however, that the proponents of breast feeding (of which I am one) overlook one of the most cogent reasons of all for feeding the newborn baby human breast milk. This is the factor of allergy. . . . The work of Grulee and Sanford, which was done long ago when there were breast feeding stations in Chicago, clearly indicated that the breast-fed baby has seven times as many chances of escaping eczema as the bottle-fed baby. In my practice, some 80 per cent of babies with eczema later develop respiratory allergies, either perennial allergic rhinitis or recurrent upper respiratory infections, which are not recognized by most pediatricians as allergic diseases or asthma or hay fever. This is a terrific percentage but I am sure of my statistics because they are worked out on cases which have been personally followed and not gathered from the literature or chance patients dropping into the office now and then.

It is also my opinion that the reason for the great increase in allergic diseases in this country is largely due to the abandonment of breast feeding during the last twenty-five or thirty years.

JEROME GLASER, M.D.

News and Notes

The following communication was received from Professor P. Plum, M.D., President of the 8th International Congress of Paediatrics, Copenhagen, 1956:

As decided at the 7th International Congress of Paediatrics in Habana, 1953, the **8th International Congress of Paediatrics** will be held in Copenhagen, Denmark, in 1956. The Congress will be opened Sunday, July 22, and closed Friday, July 27, 1956. It is planned to arrange a scientific and technical exhibition in connection with the Congress. Further information will be sent to the national paediatric associations and also published in *Acta Paediatrica* and *Helvetica Paediatrica Acta*. Address: Domus Medica, Kristianiagade, Copenhagen, Denmark.

Among the new **research grants** awarded by the **National Institute of Mental Health** upon recommendation of the National Advisory Mental Health Council, November, 1954, were:

Emanuel K. Beller. Council Child Development Center. Fear, aggression and dependency in childhood. Three years. First year $15,766.

David E. Hunt. Yale University. Effect of need for approval on children's behavior. Two years. First year $4,390.

John P. Spiegel and F. R. Kluckhohn. Harvard University. Influence of family and culture on mental health. Two years. First year $32,011.

The **Benjamin Knox Rachford Lectures** will be delivered in Cincinnati by Dr. Wolf W. Zuelzer of Detroit on March 10 and 11, 1955, at 8:30 P.M. in the Auditorium of the Children's Hospital Research Foundation.

Book Reviews

Elements of Pediatric Anesthesia. C. R. Stephen, Springfield, Ill., 1954, Charles C Thomas, Publisher, 128 pages. Price $3.50.

Dr. Stephen's new book is an excellent exposition of the principles of the use of anesthetic agents and techniques in children. Although one may differ with the author in several details, there is no misleading information in this small volume. With the increasing attention to surgery in the newborn period, further discussion in the chapter on physiological background would have been helpful, especially regarding blood volumes and blood replacement. Also, discussion of premedication during the first week of life should have been considered separately, instead of including it in an age group of 0 to 6 months. In two chapters, oxygen values of 70 to 80 per cent in inspired air are quoted, with the implication that this is a desirable concentration, whereas it is more likely undesirable. It is difficult to conceive of a situation in which more than 30 to 50 per cent oxygen is necessary. Dr. Stephen properly stresses the serious effects of low oxygen concentrations. The bibliography contains many good references.

VIRGINIA APGAR

Treatment of Acute Poliomyelitis. William A. Spencer, with 23 contributors, Springfield, Ill., 1954, Charles C Thomas, Publisher, 134 pages. Price $3.75.

Although it may be true, as stated in the foreword, that "This syllabus is neither the first nor the last word in the treatment of poliomyelitis," it is a volume which can

be read with profit by everyone engaged in the treatment of this disease. The material obviously reflects an extensive experience and a thoughtful approach to the problem of treatment. The author has carefully avoided insistence on certain doctrines of therapy and is never dogmatic. Basic physiological principles and careful clinical observation are emphasized as the keynote of successful patient care.

This book is designed for physicians of varying degrees of skill, or for the busy clinic, and is not directed primarily to the investigator. Especially valuable is the avoidance of intricate techniques of instrumental and laboratory studies of these patients and the utilization of careful bedside observation.

The clinician with great experience in this disease may disagree with some minor points of management, but will surely find this book valuable as a base line for his own program of care and for the instruction of house staff and nursing personnel in the fundamentals of treatment.

The physician with lesser experience will find this an invaluable primer, and as his own experience grows he will not find it necessary to forsake any of the principles which it lays down.

All of the material is presented succinctly and in an unusual format so well arranged as to be quickly available as new problems arise.

This book should be in every hospital ward which provides care for acute poliomyelitis. It is an entirely satisfactory authority for those clinicians with meager experience in this disease, but can profitably be perused by those with extensive knowledge.

George and John Armstrong of Castleton. William J. Maloney, M.D., LL.D., Edinburgh and London, 1954, E. & S. Livingstone, Ltd., and Baltimore, The Williams & Wilkins Co., 116 pages. Price $4.00.

Pediatricians will find a great deal of interest and enjoyment in this biography of the famous Armstrong brothers. Born and educated in Scotland, both had their medical careers in London, and, as "foreigners," had problems and difficulties in gaining recognition. While much more is known of the elder brother John, the poet-physician, it is with George, younger by ten years, and encouraged and backed by the older brother, that we are most interested. George Armstrong is credited with founding in 1769 the first children's dispensary and hospital in the world. John Ruhräh in *Pediatrics of the Past* terms him "one of the patron saints of prophylactic pediatrics," and Maloney considers him as the "father of modern pediatrics." Much of our knowledge of his life and work is due to the researches of Ernest Caulfield. Armstrong's first text, *An Essay on the Diseases Most Fatal to Infants,* is a medical classic. It was first published in 1767, and was followed by several revisions and enlargements.

The text of the biography was not in shape for publication at the time of Dr. Maloney's death in 1953, and the task fell to Dr. Poynter of the Wellcome Historical Medical Library, who most graciously assures the reader "that all that is valuable in this book is the work of its author." It is not only a scholarly biography of the Armstrong brothers, but also one that gives a most interesting picture of medical problems, practice, and intrigue two hundred years ago.

The Adolescent Exceptional Child. The Woods Schools, Langhorne, Pa., 78 pages.

The proceedings of the third Conference on the exceptional child, sponsored by the Woods Schools. The subject for this conference, held in New Orleans in 1953, in association with the Tulane University School of Medicine, was the exceptional child of adolescent age. Most of the discussion centered on the problems of placement for the retarded child of adolescent age, which include those of evaluation and training. Copies may be obtained from the Woods Schools.

L'accrescimento umano. Giovanni De Toni, Genoa, 1954, "La Scuola Editrice," 241 pages.

A text on somatic growth by Prof. De Toni. In the earlier chapters he discusses growth in the fetal period and in the child from birth to puberty. This is followed by chapters on the intrinsic (e.g., endocrine) and extrinsic (e.g., food) factors which are

involved in growth. In the latter chapters the author takes up the methods of evaluating and recording growth, with particular emphasis on the De Toni grid. The text will be of most interest to those working in the field of child development.

Pediatric Diagnosis. Morris Green, M.D., and Julius B. Richmond, M.D., Philadelphia, 1954, W. B. Saunders Co., 436 pages. Price $10.00.

This is a disappointing book. To entitle it a text on "pediatric diagnosis" is a misnomer. The authors have put together a voluminous mass of information, which, in places, even considers therapy, and have included a section on "health supervision," whose relationship to diagnosis is a puzzle the reviewer has failed to solve. Perhaps the chief fault lies in the authors' attempt to include a little of everything, and with little critical judgment in distinguishing between the important and the unimportant. For this reason, the text will be of little aid in helping reach a diagnosis by differentiation. As an example, take the discussion of abdominal pain, a most important pediatric diagnostic problem. The authors divide this into pain due to intra-abdominal and extra-abdominal causes. Under intra-abdominal they list twenty-one "intra-abdominal" causes, three splenic causes, seven liver, pancreatic, ovarian, peritonitis, mesenteric, lymphadenitis, and iliac adenitis. Under extra-abdominal are pulmonary, two cardiac, five CNS, six blood, nine metabolic, and, finally, for good measure, psychogenic. All this in six and one-half pages. Listing some half hundred conditions which cause abdominal pain, with brief or no discussion, will be of little value to the student or practitioner in reaching a diagnosis. Why, for example, a detailed discussion of the "indications for tonsillectomy" should be included in a text on diagnosis is perplexing. The book is filled with references which reflect a tremendous familiarity with medical literature, but is too lacking in judgment of the relative importance of the material included to be of much practical value. Perhaps it could be best described as a glorified *incomplete pediatrician.*

Clinical Research in Diabetes and Pregnancy. Edited by Jørgen Pedersen, M.D., Copenhagen, 1954.

A collection of papers published in 1952-1954 by Dr. Pedersen and his associates at the lying-in department of the Rigshospitalet in Copenhagen. This series of six studies includes discussions of fetal mortality, and the weight and length at birth of infants of diabetic mothers. The authors have studied a large number of pregnant women with diabetes. When the women could be intensively treated for what they term a "long time" in late pregnancy, the fetal mortality rate was much lower than when the treatment was "short time." A distinct relationship between the severity of the diabetes and the fetal mortality rate was present.

Sandoz Atlas of Haematology. Issued by Sandoz Pharmaceuticals, 68 Charlton St., New York 14, N. Y. Price $7.00.

Some five years ago Sandoz Ltd. of Basle, Switzerland, brought out an *Atlas of Haematology* with French and German texts. A new revised and enlarged edition has been published which, this time, includes a text in English. The Atlas is in loose-leaf arrangement and is divided into three parts. The first discusses basic principles and techniques. The second part contains a description of the various groups and species of blood cells. The third contains 44 plates in color of normal and abnormal cells with over 250 illustrations. Many European hematologists and clinics have contributed slides and preparations. It is a useful and practical Atlas that will be a welcome book of reference for the hospital and practitioner's laboratories.

Editors' Column

RECENT editorials on the subject of retrolental fibroplasia in the JOURNAL have stressed the necessity of accurate measurement of the oxygen concentration in the incubator used for the care of the premature infant. At the request of the Editorial Board, Dr. Jonathan T. Lanman, of the Children's Medical Service, Bellevue Hospital, and the Department of Pediatrics, New York University College of Medicine, has written the following discussion of the subject.

THE CONTROL OF OXYGEN THERAPY FOR THE PREVENTION OF RETROLENTAL FIBROPLASIA

THE relationship between oxygen therapy in premature infants and blindness due to retrolental fibroplasia (RLF) is established. Controlled studies by Patz, Hoeck, and De La Cruz[1] and Lanman, Guy, and Dancis[2] have shown that cicatricial RLF developed in a high percentage (22 per cent in each study) of infants receiving unlimited oxygen therapy, whereas none appeared in the groups receiving severely restricted treatment. A similar difference was revealed by the Cooperative Study of Retrolental Fibroplasia,[3] though the disease was not entirely eliminated from the low-oxygen group possibly because oxygen therapy was less stringently restricted. Further evidence is available from a number of other uncontrolled observations, notably a study by Gordon, Lubchenco, and Hix,[4] in which the incidence of the disease varied with the amount of oxygen administered and fell almost to zero with restricted treatment. These studies all indicate that limitation of treatment to cyanotic or distressed infants with oxygen concentrations below 40 per cent will either sharply reduce the incidence of cicatricial RLF or eliminate the disease altogether. Mortality rates have not increased with oxygen limitation.

In spite of a clear necessity to control oxygen therapy, little attention has been given to methods of accomplishing this objective. Contact with several hospitals in New York City has shown that in many cases either no control at all was exercised or that the means adopted was of dubious effectiveness. Both humanitarian and legal considerations demand an intelligent use of oxygen for premature infants. A discussion of available methods and their limitations follows.

Oxygen therapy must be limited both in *duration* and *concentration*. *Duration* of treatment is reduced by treating only those infants with demonstrable clinical need for as short a time as possible. No "routine" oxygen therapy is needed or permissible. The irregular respiratory rhythm commonly observed in premature infants is not an indication for oxygen therapy, though either oxygen or carbon dioxide may cause the rhythm to become regular. In the Bellevue Hospital unit the only recognized indication for oxygen is

cyanosis. Often only a few minutes of treatment are needed, and uninterrupted treatment never continues for more than a few hours without a test period of withdrawal. It has never been shown that any type of oxygen therapy will reduce mortality in premature infants.

The *concentration* of oxygen is usually controlled by one of three methods, each with its own advantages and limitations. The most obvious is by lowering the flow rate of 100 per cent oxygen. However, with standard oxygen equipment, the necessary flow rates of around 1 liter per minute needed in modern incubators are not accurately obtainable. Recently, specially designed flow meters accurate at low flow rates were made available, but a second problem arises. The volume of gas in some commonly used incubators is of the order of 5 cubic feet or about 150 liters. At low flow rates, some time elapses before the desired oxygen concentration is reached. If an initial period of higher flow is used, close supervision with frequent measurements of concentration is required, and a serious possibility of error is introduced. This method, therefore, seems particularly unsuited to incubators in which the lid must be raised to reach the baby and to the treatment of frequent brief cyanotic episodes.

A second method of controlling concentration is with mixing devices which dilute 100 per cent oxygen with air before delivering it to the incubator. Several such devices are marketed. They operate on the same principle as the familiar water suction pump found in most laboratories. A jet of 100 per cent oxygen blows past an open side arm through which air is sucked in to mix with the stream of oxygen. The degree of dilution is a function of the size of the openings and the pressure differentials in the system. The sizes of the openings are readily fixed, but the pressure differentials are significantly influenced by the flow rate and by back pressure created in the tubing connecting the mixing device to the incubator. In particular, changes in the length or diameter of the tubing and connecting nozzles produce large changes in the final concentration delivered to the incubator. These factors can be controlled by someone aware of their importance, but equipment must be rigidly standardized and the possibility of misapplication of these devices seems high. Recently, a device employing the same principle but eliminating many variables has been marketed.* A reducing valve supplying 100 per cent oxygen at a constant 50 pounds pressure is attached to the source of oxygen and permanently connected to a metal-mesh-covered plastic tube. This valve and tube deliver oxygen at a constant pressure to a mixing device permanently fastened to the incubator by metal fittings. The desired opening for the oxygen jet is permanently installed and can be changed only by disassembling the apparatus; and variations in flow rates through the jet from 3 to 10 liters per minute produce no appreciable change in the incubator concentration. Nursery personnel, therefore, cannot change the concentration delivered; this feature seems highly advantageous. If the device is set for a desired final concentration of 35 per cent, each liter of 100 per cent oxygen will be diluted with about 4⅓ liters of air.

*Melchior, Armstrong, Dessau Co., 730 Grand Ave., Ridgefield, N. J.

Five liters per minute flowing through the jet will, therefore, deliver about 27 liters per minute to the incubator. This is a high ventilation factor, but in our own experience there has been no trouble in maintaining desired temperatures in the incubators. Humidification creates a similar problem, but an effective humidifier can be supplied to incorporate into the high-pressure side of the device. The high ventilation rate also has certain advantages. It makes the position of incubator vents and possible leaks relatively unimportant, and in incubators with lids, concentration is rapidly restored after closing. We have been favorably impressed with this apparatus. It has been reliable in controlling oxygen concentrations and seems particularly suited for short periods of oxygen therapy where rapid achievement of desired concentrations is required. The cost of the equipment is not much greater than that of the usual apparatus for oxygen administration.

The third method of controlling oxygen concentration is with specially prepared tanks containing 60 per cent nitrogen and 40 per cent oxygen. This is the method we have used for two and one-half years at Bellevue Hospital; and with a reliable source of supply, the method seems almost foolproof. We had some initial difficulty due to the fact that our supplier tested the concentration in the tanks shortly after mixing. On delivery to our unit, we retested and found considerable deviation from the desired concentration. The supplier found that if the tanks are laid on their sides and permitted to mix by diffusion for twenty-four hours before testing, this difficulty disappears. Once the gases have mixed, no layering of the heavier oxygen beneath the nitrogen will occur at any natural environmental temperatures. The cost of this specially prepared mixture is about three times that of 100 per cent oxygen, but so little oxygen therapy is now used in our unit that this is a trivial item.

Oxygen is often given to infants in the delivery room, in ambulances during transport to premature care centers, and in the nursery to operate humidifying devices. Oxygen therapy in the delivery room appears to give no difficulty, probably because duration of treatment is short and administration equipment (often a funnel) is inefficient. Prolonged or intensive therapy should be subject to the same limitations as those applied in the premature nursery. The same applies to oxygen given during transport. Mary Crosse[5] of England has associated vascular stage lesions of RLF with excessive oxygen therapy given during several hours of transport. The New York City Health Department's Premature Transport Service limits oxygen concentration even though the trips seldom exceed forty-five minutes; such a policy is commendable.

Humidifying and aerosol devices need not be operated by oxygen. Such therapy usually lasts many hours, and when a compressed gas is needed to operate the equipment, compressed air should be used.

Incubator oxygen concentrations must be tested regularly and frequently under conditions of actual use. Unforeseen difficulties arise with any device, however simple, and variation between different incubators of the same type and even the same incubator at different times are large and unpredictable. There is no

substitute for frequent measurements of concentration, and the final test of any device to control oxygen concentration lies in repeated measurements of the incubator concentrations which it maintains. A reliable oxygen analyzer is available at below $200 and is easily operated by the nursing personnel.*

Regarding costs in general, the sharply restricted use of oxygen has resulted in significant and continuing savings in the cost of care for premature infants. Equipment to control and measure oxygen concentrations for a large premature center can be purchased for less than the average cost of caring for one infant, and this cost is repaid in a few weeks with savings from the lessened use of oxygen. The idea that expense interferes with purchase of necessary equipment is untenable. Public awareness of the cause of this devastating disease will create a difficult situation if an infant becomes blind in a hospital failing to follow recognized safe procedures. Improper use of oxygen therapy in premature infants is much less defensible than complete elimination of its use.

In summary, the proper control of oxygen use means first its total elimination except for times of clinically demonstrable need. It should then be given for as brief a time as possible at concentrations below 40 per cent. The most reliable methods for keeping the concentration below 40 per cent are: (1) the use of specially prepared cylinders of 60 per cent nitrogen-40 per cent oxygen, and (2) one particular mixing device for use with 100 per cent oxygen, described in the text and designed to eliminate the numerous variables affecting the accuracy of this type of apparatus. With any method, frequent measurement of concentrations achieved under actual operating conditions is essential. The effectiveness of strict limitation and careful control is indicated by the fact that in Bellevue Hospital none of seventy-seven surviving infants below 1,850 grams birth weight and treated by these principles has developed cicatricial RLF.

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